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Early View

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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 (AECOPD) have provided mixed results. Day-to-day variations in lung function measured by forced oscillation technique (FOT) may yield better insight. We evaluated the clinical utility of home telemonitoring of variability of FOT measures, in terms of (i) relationship with symptoms and quality of life, and (ii) 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), daily symptoms (COPD Assessment Test, CAT) and 4-weekly quality of life (St. George's Respiratory Questionnaire, SGRQ) were obtained over 8-9 months from COPD patients. Variability of resistance and reactance was calculated as the standard deviation (SD) over 7-day running windows; we also examined the effect of varying window size. The relationships between FOT versus CAT and SGRQ were assessed using linear mixed modelling, daily changes in FOT variability and CAT prior to AECOPD using one-way repeated measures ANOVA.

Results:

15 participants with mean(SD) age 69(10) years and FEV1 %predicted 39(10) had a median(IQR) adherence of 95.4(79.0–98.8)%. Variability of the inspiratory component of X (SDX_{insp}) related to CAT and weakly SGRQ (fixed effect estimate(95%CI) 1.57(0.65-2.49), p=0.001 and 4.41(-0.06–8.89), 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:

Variability of inspiratory reactance from FOT telemonitoring reflects COPD symptoms and may be a sensitive biomarker to detect AECOPD early.

Clinical trial registration: This trial was registered at www.clinicaltrials.gov as part of a larger trial NCT 01552031.

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Telemonitoring of day-to-day variations in lung function using oscillometry in COPD may help assess symptoms and detect acute exacerbations early.

Introduction (body of manuscript word count 3889 including headings)

The bulk of the significant healthcare burden from chronic obstructive pulmonary disease (COPD) is due to acute exacerbations (AECOPD)[1]. AECOPD are 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[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 quality of life, though 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, which 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 the variability. Hence, variability of FOT measures may provide a reliable way of objectively detecting AECOPD onset, and guide management[23]. In asthma, variability of FOT measures has provided the basis for markers with high sensitivity and specificity to detect 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 relate these measures to symptoms and quality of life, 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 (i) variability of FOT measures is related to symptoms and quality of life, and (ii) changes in variability of FOT measures occur with symptoms at AECOPD onset.

Methods

Subjects

Adults aged between 40-85 years with COPD, defined clinically and by FEV1/FVC<lower limit of normal and FEV1<80%predicted (GLI reference equations[26]) with ≥ten pack-year smoking history, were eligible. Exclusion criteria comprised alpha-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, 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, which recruited participants from three sites across Sydney, Australia (see Figure 1 for study protocol). At enrolment, a detailed clinical assessment including smoking and exacerbation history, medication use, as well as standard lung function measures (pre- and post-bronchodilator spirometry, plethysmographic lung volumes and diffusing capacity for carbon monoxide) were obtained according to ATS/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-measurements. For 8-9 months, each morning

before taking their inhaled COPD medication, participants recorded their symptoms by electronic COPD Assessment Test (CAT)[30] via touch-screen computer built into the FOT device. This was followed by a single, 2-minute FOT measurement during tidal breathing. If <5 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 (2G/3G) internet. Participants were called weekly to capture any changes in symptoms and/or management, and occurrence of AECOPD. Quality of life was assessed 4-weekly by telephone with St. George's Respiratory Questionnaire (SGRQ).

Exacerbation definition

An AECOPD was defined by an increase in respiratory symptoms, assessed via participant recall during the weekly telephone interview, 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 ≥7 days without treatment with corticosteroids and/or antibiotics and/or hospital admission, else they were combined as a prolonged, non-resolving exacerbation event.

Forced oscillation technique (FOT)

Measurements of respiratory system impedance were obtained using FOT at 5 Hz to derive mean respiratory resistance (R) and reactance (X). We further examined the inspiratory (R_{insp}, X_{insp}) and expiratory (R_{exp}, X_{exp}) components of resistance and reactance, and focus on reporting R_{insp} and X_{insp} though detailed results of total and

expiratory resistance and reactance can be found in the Online Supplement. In addition, we evaluated R5-19 (mean resistance at 5 Hz minus mean resistance at 19 Hz), a measure of frequency dependence of resistance, as well as DeltaX (mean inspiratory reactance at 5 Hz minus mean expiratory reactance at 5 Hz), a measure of expiratory flow limitation[31]; and breathing pattern during the FOT measurements, i.e. respiratory rate (RR) and tidal volume (Vt).

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, i.e. SD/mean of each window).

Data processing and statistical analyses

Full details of the data processing and statistical analyses can be found in the Online Supplement. Data were processed using MATLAB version 9.2. All statistical analyses were performed using R version 3.4.1., with statistical significance defined as $p<0.05$.

Relationship between variability of FOT measures, symptoms and quality of life

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 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 as 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 quality of life, separate linear mixed-effects models were again used for each FOT measure or its SD as the fixed effect, with 4-weekly SGRQ as 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 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 (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 -7 before AECOPD onset, respectively). We also used receiver-operator characteristic (ROC) curves to assess accuracy to detect AECOPD (details in Online Supplement).

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 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

19 participants attended the study enrolment visit. Two of these did not meet 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 because of technical concerns with the FOT recordings due to 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 male, mean(SD) age 69(10) years, smoking history 51(26) pack years) had moderate to severe COPD (FEV1/FVC ratio mean(SD) 34(6), FEV1 %predicted 39(10)) based on GOLD staging criteria[1] and was severely limited in their health-related quality of life as assessed by 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 at a median(IQR) of 95.4(79.0 – 98.8)%, which included one premature subject withdrawal after four months because of non-adherence (defined in our study as <50%) with the daily FOT recordings. In terms of acute exacerbations, 13/15 participants experienced a total of 37 AECOPD over the study period (mean(SD, range) 2.47(2.03, 1-6) AECOPD/subject), comprising 16 AECOPD requiring oral corticosteroids, 17 AECOPD requiring oral antibiotics, and 4 hospitalisations. The mean(SD, range) duration of an

AECOPD in the study cohort was 15.0(9.0, 4-43) days (n=35 for this analysis as the treatment period for 2 AECOPD was ongoing by the end of the study).

Relationship with symptoms

Both X_{insp} and SDX_{insp} were related to mean CAT score (fixed effect estimate (FEE)(95% CI) -0.59(-1.02–(-0.15)), p=0.009 and 1.57(0.65–2.49), p=0.001, respectively) (Table 2, Figure 2). With the exception of 3 subjects, greater SDX_{insp} was associated with higher mean CAT, i.e. more symptoms (Figure 2). Similar results were obtained with CVX_{insp} (not shown). No relationships were seen with R_{insp} or SDR_{insp} (Table S1). Measures of breathing pattern i.e. mean and variability of respiratory rate and tidal volume (RR, SDRR and Vt, CVVt), respectively, 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 (within-day variability was used for 1-day window) in our sensitivity analyses.

Relationship with quality of life

SDX_{insp} showed a borderline significant relationship with 4-weekly SGRQ (FEE 4.41(-0.06–8.89), p=0.05; Table 2, Figure 3). This result was not consistently significant when the window size was varied from 1, 5-7, 10, 14 to 28 days. No relationships were observed between inspiratory R measures, X_{insp}, CVX_{insp} or breathing pattern and SGRQ, regardless of window size (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, Figure 4). Similar results were obtained when using CV in place of SD to assess variability (Table S2). Other FOT variables (including R5-19 and DeltaX) did not change significantly prior to AECOPD (Table S3).

Notably, when 5-day and 6-day running time windows were used, the change in SDX_{insp} occurred earlier than CAT, i.e. 3 days versus 1 day prior to AECOPD onset (p=0.005, p=0.015 for SDX_{insp} and p=0.014, p=0.028 for CAT, 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 SDX_{insp} calculated over 5-day windows provided the highest accuracy (AUC=0.72) in detecting onset of AECOPD 3 days prior, out of X_{insp}, CVX_{insp} and CAT, though the ROC curve was not statistically significantly different to CAT (Figure 5, Table S4). Furthermore, combining X_{insp} and SDX_{insp} resulted in no significant changes to the AUC for SDX_{insp} alone (Delong method for comparing ROC curves, p = 0.94, 0.92 and 0.53 for 1,2 and 3 days prior, respectively).

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

Discussion

In this study, we have shown that the variability of FOT impedance measures, specifically of inspiratory reactance (SDX_{insp}, 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 window for assessing variability of FOT measures in COPD monitoring. Feasibility of COPD home telemonitoring with FOT was high, consistent with previous studies[14, 35], with high adherence (>95%) and low drop-out rates (<7%).

Relationship with patient-centred outcomes

This is the first study, to our knowledge, to evaluate the relationship between variability of FOT measures with patient-centred outcomes such as symptoms and quality of life – an essential step towards demonstrating clinical utility. Previous studies have shown mean measures of reactance to correlate with symptoms and health-related quality of life[36, 37], or to predict improvements in symptoms with bronchodilator[38], but did not examine variability. In our study, both X_{insp} and SDX_{insp} (and CVX_{insp}) showed significant relationships with symptoms. The observation that day-to-day variability, regardless of correction by mean reactance, i.e. whether expressed as SD or CV, was related to CAT 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} with respiratory quality of life was weaker. This may simply be because SGRQ was collected 4-weekly (noting it was originally validated as a 3-monthly measure) whereas CAT was assessed daily and therefore more likely to reflect the 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 inspiratory reactance were related to symptoms, we found that only variability of inspiratory reactance (SDX_{insp}, 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 occurred 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[39], and moreover perception can differ with exacerbation phenotype[40]. 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 5-7

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

Reactance parameters have been shown to reflect pathophysiological hallmark features of COPD such as hyperinflation[41], communicating lung volume[42] and expiratory flow limitation (EFL)[31]. Of note, the change to less negative reactance during inspiration distinguishes COPD from healthy subjects implying reduced heterogeneity with lung inflation during the breathing cycle[43]. Our results lend support to the idea of reactance as the more clinically relevant FOT parameter in COPD, in contrast to resistance. Furthermore, we observed the most consistent relationships in inspiratory reactance 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[42]. Thus, we speculate that increased SDX_{insp} in COPD versus health may reflect both increased magnitude of X_{insp}, via greater heterogeneity but also temporal variation in the distribution of time constants (either due to altered resistances and/or compliances within lung units), and 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; our results suggest the latter is more important for detection of AECOPD. Furthermore, perhaps the increased instability may 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 reactance.

We did not detect significant changes in the mean or variability of DeltaX pre AECOPD onset in our study cohort. There are a number of possible explanations for this. First, there may be phenotypic differences between patients – only 6 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]). Second, there may be mechanistic differences between exacerbations – some were indeed associated with increased DeltaX, but others were not, consistent with other studies[44]. To illustrate, out 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 4 had increased DeltaX 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 to detect AECOPD early[7, 8, 45]. In our study cohort, even though respiratory rate and tidal volume were strongly related to symptoms, the assessment of more detailed airway mechanics by FOT appears to demonstrate superior ability in early detection of AECOPD compared to respiratory rate and tidal volume.

Implications for further work

Our study shows that even relatively simple measures of variability (SD, 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 deteriorations 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 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 (FPR) and negative (FNR) rates across the patients who experienced AECOPD. While the median FPR and FNR were reasonable (e.g. 18.4% and 16.7%, respectively for prediction on day -3, for a 7-day window), 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; prediction may not work well in a subset of patients, either due to poor perception of symptoms (ultimately how AECOPD are defined), or these patients may have had an increase in symptoms without an associated significant change in lung function due to e.g. 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

The observational character and its small subject numbers are limitations of the presented study. Nevertheless, its results would 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 reasons. However, additional quality control could be incorporated into future automated software acquisition algorithms to flag implausibly low resistance 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 ability to detect AECOPD irrespective of severity. Also, mild exacerbations (increase in symptoms not accompanied by 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 changes from baseline. While it would have been useful to examine relative changes, to account for the influence of baseline X_{insp}, expressing the changes as relative changes 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. 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, 46], with high adherence in COPD patients[14, 47]. Here we have demonstrated, in a small COPD cohort, that variability of FOT measures reflects day-to-day symptoms and can detect AECOPD even before symptoms manifest, with higher accuracy than FOT *per se*. Thus, variability of FOT parameters may be clinically useful to assess disease status and enable early intervention of AECOPD, potentially reducing the significant healthcare burden associated with AECOPD. 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, facilitating 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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Table 1. Baseline characteristics of study participants.

	Mean(SD)	Z-score
n (male, current smoker)	15(11, 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)
FEV1 %predicted	39(10)	
FEV_1/FVC (%)	34(6)	-4.37(0.56)
DLCO %predicted[#]	34(11)	-5.28(1.93)
Total R ($cmH_2O \cdot s \cdot L^{-1}$)	4.87(1.63)	2.56(1.41)
Total X ($cmH_2O \cdot s \cdot L^{-1}$)	-3.90(1.81)	-5.79(3.00)
MRC dyspnoea score	2.80(0.94)	
CAT score	17.6(9.0)	
SGRQtotal (units)	49.3(17.9)	
Inhaled LAMA, LABA and ICS (n, %)	15(100)	
Written COPD action plan (n, %)[#]	10(67)	
$\geq$ 1 AECOPD in 12 months pre-enrolment (n, %)	11(73)	
$\geq$ 2 AECOPD in 12 months pre-enrolment (n, %)	8(53)	
1-2 AECOPD hospitalisations 12 months pre-enrolment (n, %)	8(53)	
Cardiovascular comorbidities (n, %)[##]	10(67)	

[#]n = 14 (one subject unable to perform diffusing capacity for carbon monoxide); Z-scores represent the number of standard deviations away from predicted value, calculated from Quanjer et al.[26] for spirometry and Oostveen et al.[48] for FOT measures; BMI = body mass index; FEV1 = forced expiratory volume in one second; FEV1 %predicted= percent of predicted of forced expiratory volume in one second; FEV1/FVC ratio = ratio of forced expiratory volume in one second and forced vital capacity; DLCO %predicted= percent of predicted of diffusing capacity for carbon monoxide; Total R = mean resistance; Total X = mean reactance; MRC = Medical Research Council; CAT = COPD Assessment Test; SGRQ = St. George's Respiratory Questionnaire; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta-agonist; ICS = inhaled corticosteroid; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; [##] includes hypertension and ischaemic heart disease.

Table 2. Relationship between FOT measures with symptoms (CAT) and respiratory quality of life (SGRQ).

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

Evaluation of each parameter over 7-day running window analysis period; CAT = mean score of COPD Assessment Test; SGRQ = mean total St. George's Respiratory Questionnaire score; 95% CI = 95 percent confidence interval; R_{insp} = mean inspiratory resistance; SDR_{insp} = standard deviation of inspiratory; X_{insp} = mean inspiratory reactance; SDX_{insp} = standard deviation of inspiratory reactance; RR = mean respiratory rate; SDRR = standard deviation of respiratory rate; Vt = mean tidal volume; SDVt = standard deviation of tidal volume. The fixed effect estimate represents the change in CAT or SGRQ scores per unit change in the corresponding FOT parameter.

Table 3. Timing of changes in variability of inspiratory FOT measures (assessed by standard deviation) and symptoms in the days before an AECOPD; demonstrated for 5-day to 7-day analysis windows.

		5-day window		**6-day window**		**7-day window**	
	Comparison (day before AECOPD)	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. 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	−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**

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; SE = standard error; Adj. P-value = adjusted p-value from Dunnett's post-hoc test; SDR_{insp} = standard deviation of inspiratory resistance; SDX_{insp} = standard deviation of inspiratory reactance; CAT = mean CAT score.

Figure 1. Study protocol

FEV1/FVC = forced expiratory volume in one second over 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 chronic obstructive pulmonary disease.

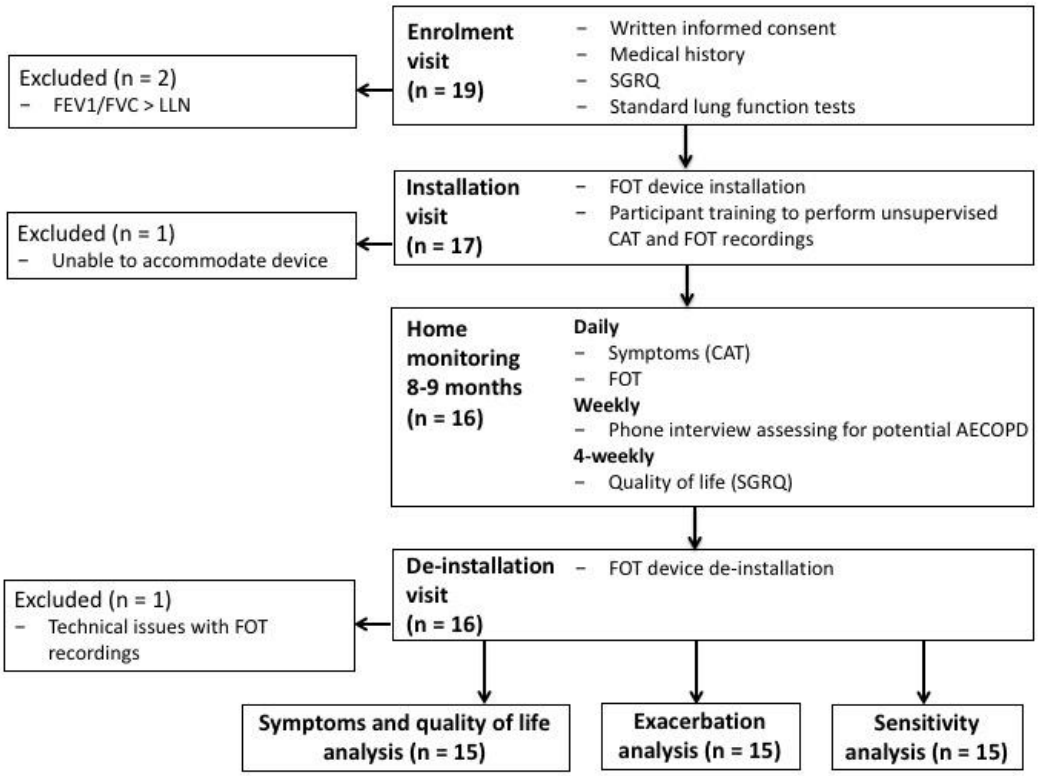


Figure 2. Relationship between variability of inspiratory reactance (SDX_{insp}) and symptoms (mean COPD Assessment Test (CAT) score), both assessed over 7-day running windows; Symbols and associated regression lines represent individual study subjects (n = 15, indicated by their study IDs 1100-1120).

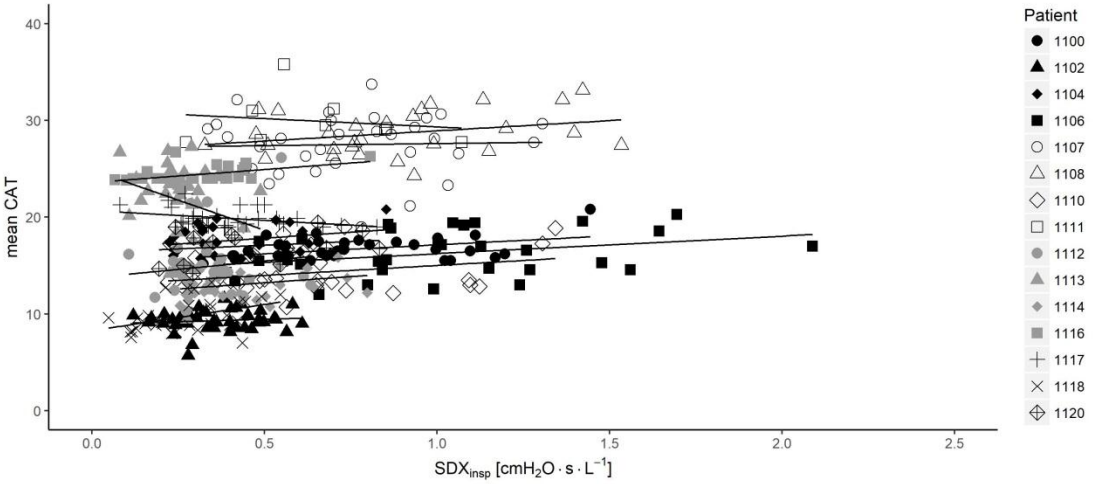


Figure 3. Relationship between variability of inspiratory reactance (SDX_{insp}) versus quality of life (St. George's Respiratory Questionnaire (SGRQ), both assessed over 7-day running windows. Symbols and associated regression lines represent individual study subjects (n = 15, indicated by their study IDs 1100-1120).

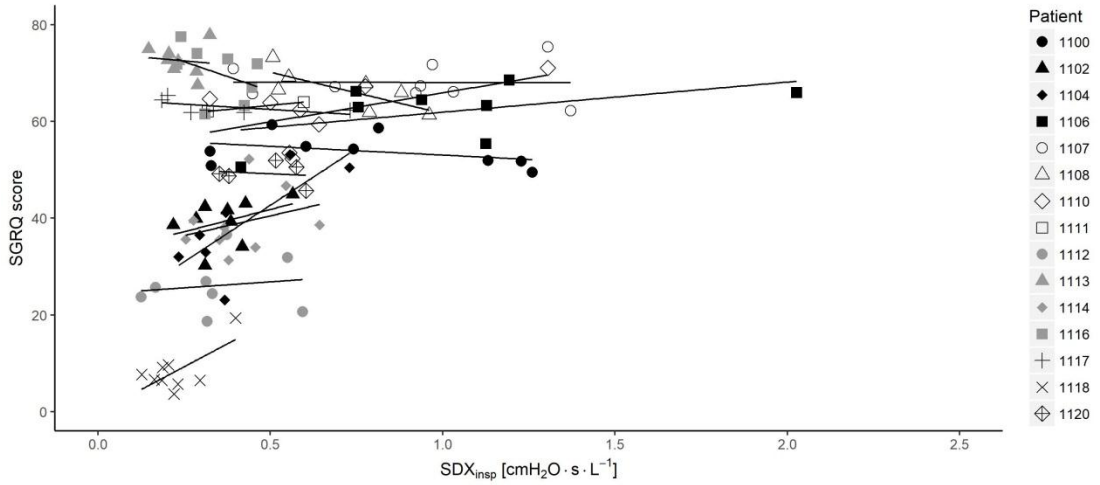


Figure 4. Timing of changes in a) mean COPD Assessment Test (CAT) score and b-d) variability of inspiratory reactance (SDX_{insp}) during the 7 days leading up to and 7 days following AECOPD using different running-window lengths including b) 5-day, c) 6-day and d) 7-day windows. Symbols and error bars correspond to the mean and standard error (SE) of the change from baseline for all pooled exacerbations (n = 37).

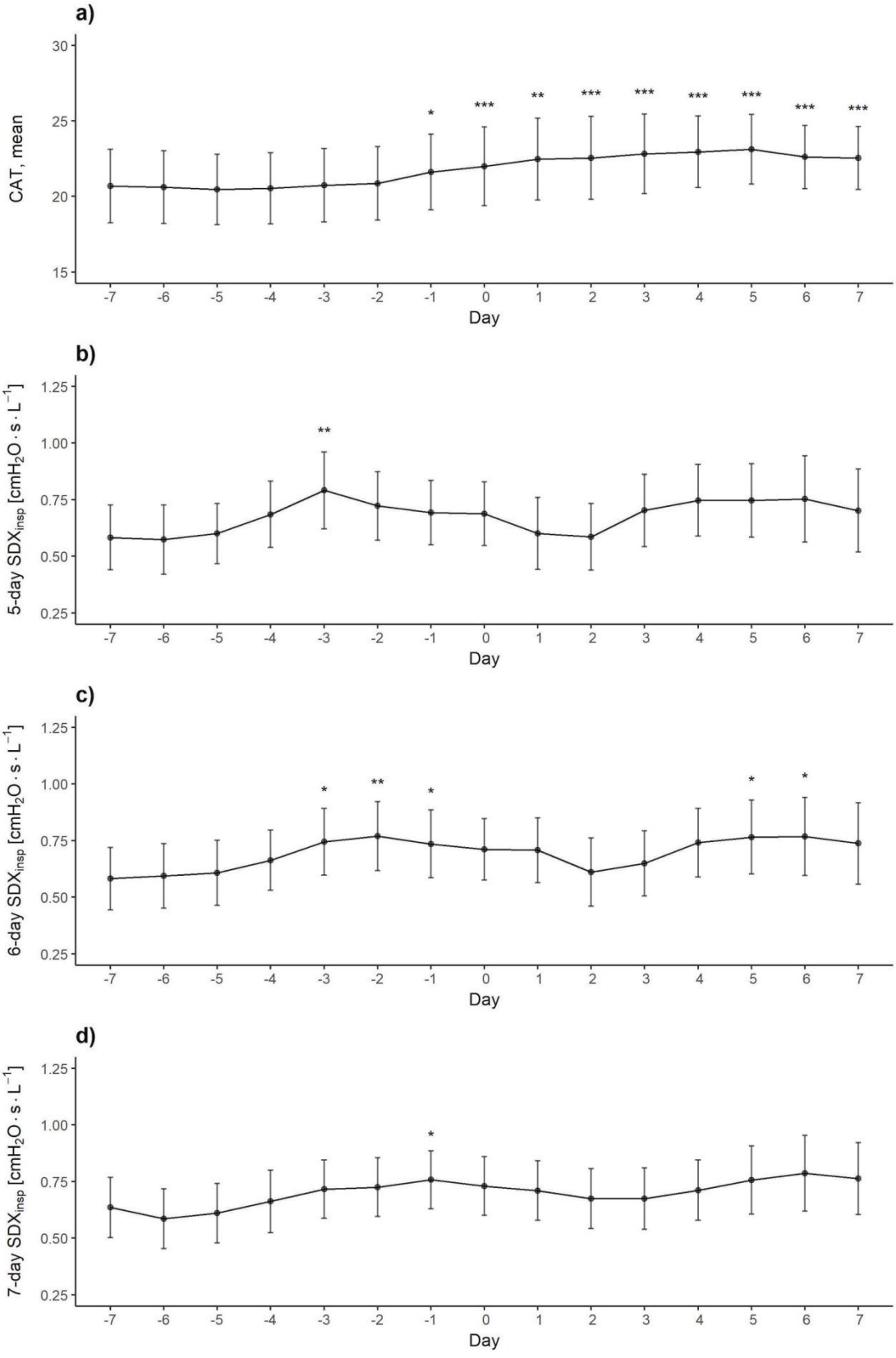
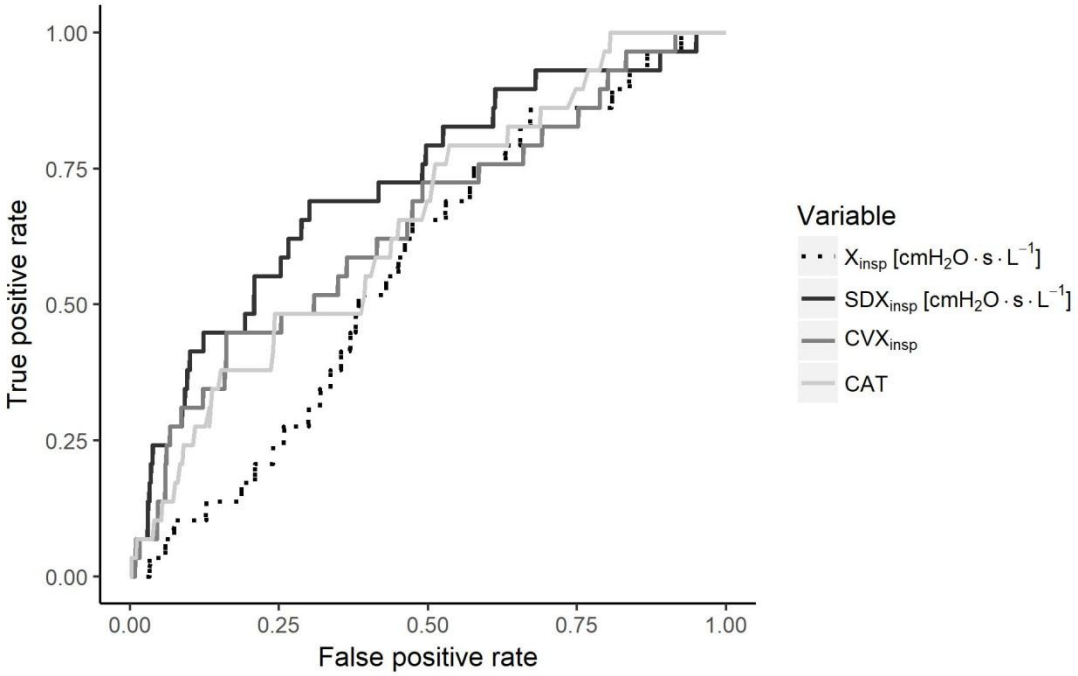


Figure 5. Receiver operating characteristic (ROC) curves for detecting acute exacerbations of chronic obstructive pulmonary disease (AECOPD) 3 days prior to onset with 5-day running windows for mean (X_{insp})and variability measures (SDX_{insp} and CVX_{insp}) of inspiratory reactance and COPD Assessment Test (CAT) score.
Area under the curve (AUC) scores: X_{insp} = 0.57, SDX_{insp} = 0.72, CVX_{insp} = 0.65, CAT = 0.65 (n= 37 AECOPD)**.**



Online Supplement

Methods

Data processing

Data were processed using MATLAB version 9.2. Daily FOT measurements and symptoms were extracted for each participant; for each FOT parameter, any days with values >3 SD from the mean for that participant over the entire trial period were removed as likely artefact. FOT 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, i.e. SD divided by mean of each window). Windows could be overlapping or non-overlapping depending on the analysis (see below). A window was excluded if >50% data were missing within that window.

Statistical analyses

All statistical analyses were performed using R version 3.4.1., with statistical significance defined as $p<0.05$. A pre-study power calculation with occurrence of AECOPD as the primary outcome identified $\geq$40 events in order to identify a predictor with a failure rate <4%, assuming power of 0.9 and α=0.05.

Relationship between variability of FOT measures, symptoms and quality of life

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 calculated within 7-day windows, for all non-overlapping windows across the entire time series for all subjects. Thus, a participant undergoing 8x4 weeks of telemonitoring would have 32 windows for analysis. Separate linear mixed-effects models were used for each FOT variable or its SD as the fixed effect, with mean weekly CAT as outcome and subject as the random effect to allow adjustment for within-subject clustering.

To assess the relationship between variability of FOT measures and quality of life, a similar approach was used, but since the SGRQ was obtained every 4 weeks, only the 7-day window prior to and including the day of SGRQ administration was examined. Thus, a participant undergoing 8x4 weeks of telemonitoring would have 8 windows for analysis. Again, separate linear mixed-effects models were used for each FOT variable or its SD as the fixed effect, with monthly SGRQ as outcome and subject as the random effect.

Timing of changes prior to AECOPD

To detect the timing of changes in variability of FOT measures and symptoms prior to an AECOPD, we examined the mean and SD of each FOT variable and the corresponding mean CAT calculated within each 7-day window in the days leading up to each AECOPD, using one-way repeated measures ANOVA. For this analysis, overlapping running windows were used to enable us to examine these changes with a finer time resolution, i.e. of 1 day. AECOPD from all patients were pooled and aligned, with some participants experiencing more than 1 AECOPD. Each onset of AECOPD was assigned as day 0 (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 -7 before AECOPD onset, respectively). This assumes a stable baseline, i.e. that any changes leading up to an AECOPD would not have occurred as early as 7 days prior to the AECOPD, and that the effects of any previous AECOPD had resolved. The windowing proceeded in a similar manner for the rest of the period prior to AECOPD, i.e. day -6 corresponds to the period from day -12 to -6.

Sensitivity analyses

We chose a 7-day running window size for the assessment of FOT variability measures based on previous similar work in asthma, for both PEF[28, 29] and FOT[22]. For each analysis in this study, we also evaluated the effect of varying this window size on the results.

ROC Analysis

We evaluated the ability of the main variables of interest from our results to respectively detect AECOPD using observation windows at 1, 2 and 3 days prior to the AECOPD. We applied a 5-day running window, and extracted the mean X_{insp}, SDX_{insp}, CVX_{insp} and mean CAT from those which satisfied the quality criteria (> 50% data availability). Windows including the period of AECOPD itself were excluded from observation window calculations, to remove the potential confounding effect of the AECOPD on the variables during the AECOPD. We then generated receiver-

operator characteristic (ROC) curves and evaluated the following metrics: the area under ROC curve (AUC) as a measure of predictive ability, the optimum threshold for maximising the sensitivity and specificity (using the Youden Index (J)), and the corresponding sensitivity and specificity at this threshold (Table S4). AUCs for X_{insp}, SDX_{insp}, and CVX_{insp} were compared respectively against the AUC for mean CAT using the Delong method for two-sided comparison of paired ROCs.

Table S1. Relationships between mean FOT impedance and FOT impedance variability measures with symptoms (CAT) and respiratory quality of life (SGRQ).

	CAT		SGRQ	
	Fixed Effect Estimate (95% CI)	**P-value**	**Fixed Effect Estimate (95% CI)**	**P-value**
R	-0.245 (-0.529–0.038)	0.09	0.197 (-1.258–1.652)	0.79
R_{insp}	0.002 (-0.37–0.37)	0.99	0.27 (-1.73–2.27)	0.79
R_{exp}	**-0.275(-0.514– (-0.0358))**	**0.02**	0.186 (-1.040–1.412)	0.76
SDR	-0.022 (-0.814–0.771)	0.96	0.946 (-3.157–5.050)	0.65
SDR_{insp}	0.43 (-0.38–1.24)	0.30	3.39 (-1.11–7.89)	0.14
SDR_{exp}	-0.115 (-0.824-0.594)	0.75	-0.242 (-3.739–3.256)	0.89
X	-0.166 (-0.389–0.058)	0.15	-0.350 (-1.525–0.825)	0.56
X_{insp}	**-0.59 (-1.02–(-0.15))**	**0.009**	-1.30 (-3.55–0.94)	0.25
X_{exp}	-0.096 (-0.266–0.0739)	0.27	-0.183 (-1.081–0.715)	0.69
SDX	0.197 (-0.433–0.827)	0.54	**3.585(0.274–6.897)**	**0.03**
SDX_{insp}	**1.57 (0.65–2.49)**	**0.001**	**4.41 (-0.06–8.89)**	**0.05**
SDX_{exp}	0.039 (-0.469–0.547)	0.88	2.774 (-0.072–5.620)	0.06

Evaluation of each parameter over 7-day running window analysis period; CAT = mean score of COPD Assessment Test; SGRQ = mean score of total St. George's Respiratory Questionnaire score; 95% CI = 95 percent confidence interval; R = mean total resistance; R_{insp} = mean inspiratory resistance; R_{exp} = mean expiratory resistance; SDR = standard deviation of total resistance; SDR_{insp} = standard deviation of inspiratory resistance; SDR_{exp} = standard deviation of expiratory resistance; X = mean total reactance; X_{insp} = mean inspiratory reactance; X_{exp} = mean expiratory reactance; SDX = standard deviation of total reactance; SDX_{insp} = standard deviation of inspiratory reactance; SDX_{exp} = standard deviation of expiratory reactance. The fixed effect estimate represents the change in CAT or SGRQ scores per unit change in the corresponding FOT parameter.

Table S2. Timing of changes in variability of inspiratory FOT measures (assessed by coefficient of variation (CV) and symptoms in the days before an AECOPD, for the 5-day to 7-day analysis windows.

		5-day window		**6-day window**		**7-day window**	
	Comparison (day before AECOPD)	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. P-value
CVR_{insp}	−3	0.011 (0.011)	0.86	0.006 (0.010)	0.99	-3.10^{-4} (0.009)	1.00
	−2	-0.003 (0.011)	1.00	0.006 (0.010)	0.98	0.004 (0.009)	1.00
	−1	-3.00^{-5} (0.011)	1.00	-0.004 (0.010)	1.00	0.005 (0.009)	0.99
	0	2.20^{-5} (0.011)	1.00	0.001 (0.010)	1.00	-3.11^{-5} (0.009)	1.00
CVX_{insp}	**−3**	**0.075 (0.025)**	**0.014**	**0.056 (0.020)**	**0.028**	0.028 (0.016)	0.350
	−2	0.054 (0.025)	0.134	**0.073 (0.020)**	**0.002**	0.035 (0.016)	0.139
	−1	0.046 (0.025)	0.274	**0.060 (0.020)**	**0.017**	**0.054 (0.016)**	**0.005**
	0	0.057 (0.025)	0.114	**0.057 (0.020)**	**0.026**	**0.044 (0.016)**	**0.036**
CAT	−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**

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; SE = standard error; Adj. P-value = adjusted p-value from Dunnett's post-hoc test; CVR_{insp} = coefficient of variation of inspiratory resistance; CVX_{insp} = coefficient of variation of inspiratory reactance; CAT = mean COPD Assessment Test score.

Table S3. Timing of changes in total and within-breath FOT measures in the days before an AECOPD for the 5-day to 7-day analysis windows.

		5-day window		**6-day window**		**7-day window**	
	Comparison (day before AECOPD)	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. P-value	Mean difference (SE)	Adj. P-value
R ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.054 (0.082)	0.98	-0.099 (0.069)	0.55	-0.101 (0.064)	0.44
	−2	0.002 (0.082)	1.00	-0.082 (0.069)	0.73	-0.112 (0.064)	0.33
	−1	-0.018 (0.082)	1.00	-0.031 (0.069)	1.00	-0.095 (0.064)	0.50
	0	0.049 (0.083)	0.99	-0.016 (0.070)	1.00	-0.040 (0.064)	0.99
R_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.062 (0.091)	0.98	-0.116 (0.074)	0.46	-0.123 (0.068)	0.29
	−2	0.012 (0.090)	1.00	-0.105 (0.074)	0.56	-0.144 (0.068)	0.16
	−1	-0.042 (0.091)	1.00	-0.040 (0.074)	0.99	-0.126 (0.067)	0.27
	0	-2.9^{-4} (0.091)	1.00	-0.072 (0.075)	0.87	-0.081 (0.068)	0.72
R_{exp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.055 (0.085)	0.98	-0.094 (0.072)	0.64	-0.082 (0.066)	0.70
	−2	-0.019 (0.084)	1.00	-0.084 (0.071)	0.74	-0.098 (0.066)	0.52
	−1	-0.021 (0.085)	1.00	-0.039 (0.071)	0.99	-0.080 (0.066)	0.71
	0	0.065 (0.085)	0.96	0.001 (0.072)	1.00	-0.019 (0.067)	1.00
R5-19 ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.027 (0.069)	1.00	-0.056 (0.056)	0.86	-0.087 (0.052)	0.38
	−2	0.024 (0.068)	1.00	-0.047 (0.056)	0.93	-0.089 (0.052)	0.36
	−1	-0.026 (0.069)	1.00	-0.016 (0.056)	1.00	-0.080 (0.052)	0.46
	0	-0.018 (0.069)	1.00	-0.063 (0.057)	0.78	-0.073 (0.052)	0.58
SDR ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.053 (0.056)	0.88	-0.029 (0.048)	0.99	-0.068 (0.041)	0.38
	−2	-0.081 (0.055)	0.53	-0.003 (0.048)	1.00	-0.015 (0.041)	1.00
	−1	-0.045 (0.056)	0.95	-0.036 (0.048)	0.96	0.006 (0.040)	1.00
	0	0.025 (0.056)	1.00	0.032 (0.048)	0.98	0.019 (0.041)	1.00

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
SDR_{exp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.053 (0.056)	0.88	-0.029 (0.048)	0.99	-0.068 (0.041)	0.38
	−2	-0.081 (0.055)	0.53	-0.003 (0.048)	1.00	-0.015 (0.041)	1.00
	−1	-0.045 (0.056)	0.95	-0.036 (0.048)	0.96	0.006 (0.041)	1.00
	0	0.025 (0.056)	1.00	0.032 (0.048)	0.98	0.019 (0.041)	1.00
SDR5-19 ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.014 (0.040)	1.00	-0.018 (0.035)	1.00	-0.032 (0.031)	0.84
	−2	-0.022 (0.039)	0.99	0.004 (0.034)	1.00	-0.035 (0.031)	0.78
	−1	-0.056 (0.040)	0.57	-0.046 (0.034)	0.62	-0.019 (0.031)	0.98
	0	-0.057 (0.040)	0.54	-0.052 (0.035)	0.51	-0.046 (0.031)	0.52
X ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.188 (0.096)	0.22	0.134 (0.081)	0.39	0.113 (0.108)	0.83
	−2	0.076 (0.095)	0.94	0.193 (0.080)	0.08	0.103 (0.108)	0.88
	−1	0.090 (0.096)	0.89	0.090 (0.080)	0.77	0.153 (0.108)	0.56
	0	0.129 (0.096)	0.61	0.145 (0.081)	0.31	0.113 (0.109)	0.83
X_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.027 (0.091)	1.00	0.027 (0.077)	1.00	0.027 (0.068)	1.00
	−2	-0.019 (0.090)	1.00	0.058 (0.077)	0.96	0.044 (0.068)	0.98
	−1	0.002 (0.091)	1.00	0.062 (0.077)	0.94	0.108 (0.068)	0.44
	0	0.011 (0.091)	1.00	0.052 (0.077)	0.98	0.081 (0.068)	0.73
X_{exp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.100 (0.195)	1.00	0.153 (0.155)	0.86	0.182 (0.132)	0.59
	−2	0.004 (0.193)	1.00	0.153 (0.154)	0.86	0.179 (0.132)	0.60
	−1	-0.042 (0.196)	1.00	0.128 (0.154)	0.93	0.218 (0.131)	0.39
	0	-0.112 (0.196)	0.99	0.073 (0.156)	1.00	0.170 (0.132)	0.66

DeltaX ($cmH_2O \cdot s \cdot L^{-1}$)	−3	-0.027 (0.148)	1.00	-0.091 (0.113)	0.94	-0.096 (0.092)	0.83
	−2	0.047 (0.146)	1.00	-0.040 (0.112)	1.00	-0.058 (0.092)	0.98
	−1	0.102 (0.148)	0.98	-0.016 (0.122)	1.00	-0.036 (0.092)	1.00
	0	0.170 (0.148)	0.76	0.020 (0.113)	1.00	-0.019 (0.093)	1.00
SDX ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.188 (0.096)	0.22	0.134 (0.081)	0.31	0.097 (0.068)	0.55
	−2	0.076 (0.095)	0.94	0.193 (0.080)	0.08	0.136 (0.068)	0.21
	−1	0.090 (0.096)	0.86	0.090 (0.080)	0.77	0.173 (0.067)	0.06
	0	0.129 (0.096)	0.61	0.145 (0.081)	0.31	0.139 (0.068)	0.19
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
SDX_{exp} ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.183 (0.117)	0.45	0.126 (0.099)	0.67	0.079 (0.086)	0.90
	−2	0.036 (0.116)	1.00	0.186 (0.099)	0.26	0.110 (0.086)	0.66
	−1	0.080 (0.117)	0.98	0.064 (0.099)	0.98	0.151 (0.086)	0.32
	0	0.128 (0.117)	0.80	0.153 (0.100)	0.47	0.134 (0.087)	0.46
SDDeltaX ($cmH_2O \cdot s \cdot L^{-1}$)	−3	0.014 (0.095)	1.00	-0.002 (0.081)	1.00	0.021 (0.067)	1.00
	−2	-0.015 (0.094)	1.00	0.064 (0.081)	0.95	0.054 (0.067)	0.94
	−1	0.009 (0.095)	1.00	0.011 (0.081)	1.00	0.076 (0.067)	0.77
	0	0.039 (0.095)	1.00	0.050 (0.082)	0.99	0.082 (0.068)	0.72

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; SE = standard error; Adj. p-value = adjusted p-value from Dunnett's post-hoc test; R = mean total resistance; R_{insp} = mean inspiratory resistance; R_{exp} = mean expiratory resistance; R5-19 = measure of frequency dependence of resistance; SDR = standard deviation of total resistance; SDR_{insp} = standard deviation of inspiratory resistance; SDR_{exp} = standard deviation of expiratory resistance; SDR5-19 = standard deviation of measure of frequency dependence of resistance; X = mean total reactance; X_{insp} = mean inspiratory reactance; X_{exp} = mean expiratory reactance; DeltaX = expiratory flow limitation index as measured by forced oscillometry; SDX = standard deviation

of total reactance; SDX_{insp} = standard deviation of inspiratory reactance; SDX_{exp} = standard deviation of expiratory reactance; SDDeltaX = standard deviation of expiratory flow limitation index as measured by forced oscillometry.

Table S4. Summary of Receiver Operating Characteristic (ROC) analysis with 5-day running windows for selected FOT variables and CAT, evaluating accuracy in detecting an AECOPD at 1, 2 or 3 days prior.

Variable	Day(s) prior to AECOPD	AUC	P	Youden's J Statistic	Threshold	Sensitivity	Specificity
X_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	1	0.56	0.21	0.16	-2.83	0.64	0.51
SDX_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	1	0.68	0.91	0.31	0.55	0.61	0.70
CVX_{insp}	1	0.62	0.51	0.23	0.15	0.82	0.40
CAT	1	0.67		0.29	25.37	0.43	0.86
X_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	2	0.58	0.41	0.18	-2.55	0.73	0.45
SDX_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	2	0.69	0.43	0.34	0.59	0.60	0.74
CVX_{insp}	2	0.63	0.79	0.24	0.14	0.87	0.37
CAT	2	0.64		0.23	25.55	0.37	0.87
X_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	3	0.57	0.27	0.19	-2.03	0.86	0.33
SDX_{insp} ($cmH_2O \cdot s \cdot L^{-1}$)	3	0.72	0.30	0.39	0.55	0.69	0.70
CVX_{insp}	3	0.65	0.98	0.29	0.30	0.45	0.84
CAT	3	0.65		0.26	16.23	0.79	0.46

AECOPD = acute exacerbation of chronic obstructive pulmonary disease; AUC = area under the curve score; X_{insp} = mean inspiratory reactance; SDX_{insp} = standard deviation of inspiratory reactance; CVX_{insp} = coefficient of variation of inspiratory reactance; CAT = mean COPD Assessment Test score; P = p-value corresponding to comparison with the ROC curve for CAT.