

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 ≥ 40 events in order to identify a predictor with a failure rate $< 4\%$, assuming power of 0.9 and $\alpha = 0.05$.

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 ₂ O's·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 ₂ O's·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 ₂ O's·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 ₂ O's·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 ₂ O's·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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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 ₂ O's'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; $SD\Delta X$ = 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 ₂ O's·L ⁻¹)	1	0.56	0.21	0.16	-2.83	0.64	0.51
SDX_{insp} (cmH ₂ O's·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 ₂ O's·L ⁻¹)	2	0.58	0.41	0.18	-2.55	0.73	0.45
SDX_{insp} (cmH ₂ O's·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 ₂ O's·L ⁻¹)	3	0.57	0.27	0.19	-2.03	0.86	0.33
SDX_{insp} (cmH ₂ O's·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.