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Measurement of Physiological Recovery from Exacerbation of Chronic Obstructive Pulmonary Disease using Within-breath Forced Oscillometry

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ABSTRACT

Introduction:- Within-breath reactance from forced oscillometry estimates resistance via its inspiratory component ($X_{rs,insp}$) and flow limitation via its expiratory component ($X_{rs,exp}$). This study assessed whether reactance could detect recovery from an exacerbation of chronic obstructive pulmonary disease (COPD).

Method:- Thirty-nine COPD subjects with an exacerbation were assessed on three occasions over six weeks using post-bronchodilator forced oscillometry, arterial blood gases, spirometry including inspiratory capacity, symptoms and health related quality of life (HRQOL).

Results:- Significant improvements were seen in all spirometric variables except the ratio of forced expiratory volume in 1 second (FEV_1) and vital capacity (VC), ranging in mean (SEM) size from 11.0 (2.2) % predicted for peak expiratory flow to 12.1 (2.3) % predicted for VC at 6 weeks. There was an associated increase in arterial partial pressure of oxygen (P_aO_2). There were significant mean (SEM) increases in both $X_{rs,insp}$ and $X_{rs,exp}$ (27.4 (6.7) % and 37.1 (10.0) % respectively) but no change in oscillometry resistance (R_{rs}) values. Symptom scales and HRQOL scores improved. For most variables the largest improvement occurred within the first week with spirometry having the best signal to noise ratio. Changes in symptoms and HRQOL correlated best with changes in FEV_1, P_aO_2 and $X_{rs,insp}$.

Conclusions:- The physiological changes seen following an exacerbation of COPD comprised both an improvement in operating lung volumes and a reduction in airway resistance. Given the ease with which forced oscillometry can be performed in these subjects, measurements of $X_{rs,insp}$ and $X_{rs,exp}$ could be useful for tracking recovery.

INTRODUCTION

Changes in lung function, symptoms and health related quality of life (HRQOL) during exacerbations of chronic obstructive pulmonary disease (COPD) have previously been evaluated. Lung function has been assessed by peak expiratory flow (PEF)[1][2] and spirometry.[1][3][4] The largest rates of change occurred in the first few days of the exacerbation with greater increases in FEV_1 over the first two days being predictive of superior clinical outcome.[5] Recovery was sometimes slow and incomplete with only 75% having regained their original PEF by 35 days after the exacerbation and 7.1% not returning to baseline lung function at 3 months.[1] Changes in symptoms have been determined using patient diaries,[1][6] with the onset of symptoms occurring before changes in lung function.[1] Improvement in disease specific HRQOL following a transient fall due to an exacerbation has been demonstrated using the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ).[2][7][8] Improvement in HRQOL following an exacerbation has been shown to be curtailed if a further exacerbation occurs during recovery.[9]

Forced oscillometry is a method of measuring the resistive properties of the respiratory system which can delineate within-breath changes with sub-second resolution.[10] Its output is commonly expressed as two variables, resistance (R_{rs}) and reactance (X_{rs}), which represent the spectral relationship between pressure and flow of a low amplitude sinusoidal forcing signal entrained in the air which the subject breathes. R_{rs} is derived from the in phase relationship and is thought to be a direct estimate of resistance. X_{rs} is calculated from the out of phase relationship. In normal subjects it is thought to reflect elastic and inertive properties but in subjects with airways obstruction inspiratory values of X_{rs} have a stronger linear relationship with transpulmonary resistance than do the equivalent R_{rs} values.[11] In addition, expiratory values of X_{rs} have been used to establish the presence of expiratory flow limitation.[12][13]

Forced oscillometry may be particularly appropriate for the objective physiological assessment of patients with an exacerbation of COPD. It is a passive manoeuvre which requires only tidal breathing and is easily performed by breathless subjects. Further, within-breath measurements of X_{rs} could be used to estimate simultaneously both airway resistance and degree of expiratory flow limitation. To date only one study has reported forced oscillometry data during an exacerbation of COPD.[14] This confirmed the expectation that R_{rs} would not change but that X_{rs} would rise significantly towards more normal values as the exacerbation resolved. Within breath X_{rs} data during an exacerbation of COPD have not been reported.

The aim of this study was to assess the ability of within-breath forced oscillometry to detect longitudinal physiological changes during an exacerbation of COPD in comparison with spirometry, gas exchange, symptoms and HRQOL.

METHODS

Subjects

Patients with a clinical diagnosis of COPD admitted to the medical receiving ward or referred to the Acute Respiratory Assessment Service at Glasgow Royal Infirmary (GRI) were approached to take part in the study. They were within 48 hours of the point of presentation when first assessed, age > 40 years, smoking history > 20 pack-years and had baseline spirometry which satisfied the British Thoracic Society definition of COPD (i.e. FEV_1 < 80% predicted and FEV_1 to forced vital capacity ratio < 70%).[15] They had recognised features of an exacerbation, the criteria used here being increased breathlessness for at least 24 hours with at least two of increased cough frequency or severity, increased sputum volume or purulence or increased wheeze.[16] The only exclusion criterion was decompensated respiratory failure.

To detect a change in R_{rs} of ~0.05 kPa.s.L^{-1} with 80% power and a significance level of 0.05, the sample size required was 35 assuming a standard deviation for the change of ~0.15 kPa.s.L^{-1}. Given that some attrition was expected because of the frail condition of the study subjects, it was decided to aim for 50 patients in total. Ethical approval for this study was obtained from the GRI Local Research & Ethics Committee (Glasgow, UK) and written informed consent was given by each subject.

Study Design

This was a longitudinal observational study (summarised in Figure 1). At the start of each visit the subject received 5 mg of nebulised salbutamol delivered over 10 to 15 minutes in a 2.5 ml volume using a jet nebulizer (Micro-Neb Nebuliser, Lifecare Hospital Supplies, Market Harborough, UK) driven by an airflow of 8 L.min^{-1} (Aquilon Nebuliser System, AFP Medical, Rugby, UK) through a face mask (Duo Mask Adult, Lifecare Hospital Supplies). Measurements were performed 20 minutes after the nebulised salbutamol had been given. Visit 2 was scheduled to occur at approximately one week following visit 1 and visit 3 at 6 weeks. If the patient suffered a relapse between visits 2 and 3 which required hospital admission or further treatment by the Hospital at Home team, visit 3 was postponed until the patient was in a stable condition at home and on normal treatment. One operator (MKJ) performed all tests and was blinded to the results of earlier tests.

Physiological Measurements

Spirometry was performed using a laptop-based spirometer (KoKo Spirometer, Ferraris Respiratory, Louisville, USA). The variables measured were slow vital capacity (VC), FEV_1, FEV_1/VC ratio, inspiratory capacity (IC) and PEF. Quality control and procedures of testing followed the guidelines of the European Respiratory Society endorsed by the British Thoracic Society and the Association of Respiratory Technology and Physiology.[17][18] Results of at least three satisfactory manoeuvres were obtained and the reported values were the highest value for FEV_1, VC and PEF and the mean result for FEV_1/VC. IC was measured during a

slow expiratory VC manoeuvre where a period of tidal breathing was followed by inspiration to total lung capacity to record IC and then a full expiration to residual volume to give VC. Performance of this procedure was checked visually and repeated until two IC values were within 10% of each other. The average of these two values was used. Predicted normal values were calculated using the European Community for Steel and Coal (ECSC) equations.[17] Predicted IC was calculated by subtracting predicted functional residual capacity from predicted total lung capacity.

Sampling of earlobe arterialised capillary blood was performed to obtain values for arterial partial pressure of oxygen (P_aO_2) and carbon dioxide (P_aCO_2).[19] A nicotinate vasodilator cream (Transvasin, SSL International plc, Knutsford, UK) was applied to the earlobe 20 minutes prior to blood sampling. The earlobe was then punctured using a 21G needle, blood was collected into a heparinised 140µL capillary tube (Multicap, Bayer Diagnostics, Sudbury, UK) and analysed immediately on an arterial blood gas analyser (Chiron Diagnostics Rapidlab 865, Halstead, UK).

The method for forced oscillometry has been described in detail elsewhere[11] and followed the recently published European Respiratory Society recommendations.[10] While the subject performed tidal breathing through a mouthpiece with nose occluded and cheeks supported, the oscillometer performed within-breath measurements of the impedance of the respiratory system (Z_{rs}) using a sinusoidal excitation signal of 5 Hz frequency generated by a loudspeaker. A bias flow of 0.25 $L.s^{-1}$ of air was fed into the breathing circuit in order to minimise rebreathing. Calculation of Z_{rs} was performed by software. The breathing and forcing waveforms were separated using a moving average filter[20] and Z_{rs} was calculated from the forcing waveforms using the method based upon power spectra[21] further adapted for within-breath analysis.[20] This was separated into R_{rs} and X_{rs} and calculated as a function of time at each digitisation point (sampling frequency of 200 Hz) using the 0.2 s interval of flow and pressure centred on that point. These within breath values were low pass filtered to remove biological noise using a Butterworth eight-pole filter with a cut-off frequency of 2 Hz. The R_{rs} and X_{rs} values were averaged over the inspiratory ($R_{rs,insp}$, $X_{rs,insp}$) and expiratory ($R_{rs,exp}$, $X_{rs,exp}$) phases of each breath to give separate values for the two phases of the respiratory cycle. The studies by Dellaca et al.[12][13] showed that in COPD subjects the difference between mean values of inspiratory and expiratory reactance (i.e. ΔX_{rs} which equals $X_{rs,insp} - X_{rs,exp}$) could detect expiratory flow limitation proven by oesophageal manometry with high sensitivity and specificity. In the later study[13], $\Delta X_{rs} > 0.275$ $kPa.s.L^{-1}$ had a sensitivity of 95% and specificity of 98% for detecting breaths as flow-limited. Percentage flow limitation (%FL), which represents the proportion of breaths for which ΔX_{rs} indicated flow limitation, was calculated for the subjects in this study. For all oscillometry variables, values from two recordings of one minute duration were averaged.

Symptom Scales and Health Related Quality of Life Questionnaires

Symptoms were assessed using visual analogue scales for sleep, wheeze and mobility derived from Davies[16] and a numerical scale used by Paggiaro.[22] Dyspnoea was measured by four scales: visual analogue scale (VAS),[16] modified Borg score,[23] oxygen cost diagram (OCD)[24] and the Baseline and Transitional Dyspnoea Indices (BDI/TDI).[25] Activities of daily living (ADLs) were assessed using the London Chest Activities of Daily Living Questionnaire (LCADL).[26] HRQOL was assessed using the St George's Respiratory Questionnaire (SGRQ).[27]

Statistical Analysis

Baseline results were summarised either as mean (standard deviation: SD) or median (range) and changes as mean ± standard error of the mean (SEM). The changes in each test parameter were analysed between visit 2 and visit 1, visit 3 and visit 1 and visit 3 and visit 2 using the Student paired t test. To compare the relative utility of each variable, a sensitivity index[28] was calculated from the size of the change divided by the coefficient of variation.[29] To assess the relationship between changes in physiological variables and symptoms or HRQOL, Pearson correlation coefficients were calculated for changes in the key variables between visit 1 and visit 3. The level of statistical significance was taken as 0.05 throughout. All statistics were performed with Statview v 5.0.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subjects

The recruitment of subjects into this study is summarised in Figure 2. Eighty six subjects with COPD were approached to take part. Of the 50 subjects who consented, 5 were excluded (3 by spirometry showing absence of airways obstruction and 2 were non-smokers with bronchiectasis). A further 6 failed to attend after the first visit, leaving evaluable data on 39 subjects. The subjects successfully completed all the study protocol at the visits they attended and all had airways obstruction at their final visit after recovery from the exacerbation.

Baseline Results

The data in Table 1 summarise the physiological status of the subjects at visit 1. Mean spirometry values showed moderate airways obstruction with a reduced inspiratory capacity similar to values elsewhere.[2] Approximately half the subjects were in respiratory failure (mainly Type 1). The oscillometry results showed increased magnitude of R_{rs} and X_{rs} compared with normal values[10]. Expiratory flow limitation (indicated by ΔX_{rs}) was present to some degree in 37 of the 39 subjects at Visit 1. If expiratory flow limitation were present, not all breaths were necessarily affected, the proportion ranging from 0 to 100% with a mean of 68% (Table 1). The number showing flow limitation dropped on subsequent visits to 30 of 37 subjects at visit 2 and 24 of 36 subjects at visit 3. The patients were more symptomatic than normal reflected by their VAS scores for sleep, wheeze and mobility and by their values on the TDI scale. Activities of daily living were severely impaired and HRQOL was poor, with SGRQ values higher than those quoted by Spencer.[7]

Table 1. Baseline values from visit 1. All data are mean (SD) unless otherwise indicated.

			Baseline Values
No (No male)			39 (16)
Age (years)			63.1 (6.9)
No with BMI <25 : 25-30 : >30			19 : 13 : 7
Smoking history			
- **ex or current smokers : lifelong non-smokers**			39:0
- **pack years**			40 (10-100)[+]
Time interval (days)			
- **admission to visit 1**			2 (0 - 3) [+]
- **visit 1 to visit 2**			7 (3 - 15) [+]
- **visit 1 to visit 3**			42 (35 - 102) [+]
Spirometry			
VC	**L**		2.45 (0.90)
	% pred		88 (25)
FEV_1	**L**		0.96 (0.42)
	% pred		43 (16)
FEV_1/VC	**%**		40 (10)
PEF	**$L.s^{-1}$**		2.75 (1.11)
	% pred		43 (16)
IC	**L**		1.70 (0.65)
	% pred		77 (28)
Capillary earlobe blood gases			
P_aO_2	**kPa**		8.07 (1.35)
P_aCO_2	**kPa**		4.74 (0.77)
Breathing pattern			
Respiratory rate		**min^{-1}**	19.3 (5.6)
Tidal volume		**L**	0.737 (0.249)

[+] Median (range)

Table 1 (continued)

		Baseline Values
Oscillometry		
R_{rs}	**kPa.s.L^{-1}**	0.605 (0.194)
X_{rs}	**kPa.s.L^{-1}**	-0.594 (0.269)
$R_{rs,insp}$	**kPa.s.L^{-1}**	0.517 (0.152)
$X_{rs,insp}$	**kPa.s.L^{-1}**	-0.298 (0.117)
$R_{rs,exp}$	**kPa.s.L^{-1}**	0.658 (0.231)
$X_{rs,exp}$	**kPa.s.L^{-1}**	-0.776 (0.389)
%FL	**%**	68 (35)
Symptom score		
VAS		
Sleep		-37.6 (42.7)
Wheeze		-39.4 (36.0)
Mobility		-65.8 (34.5)
Paggiaro		9.18 (2.73)
Dyspnoea		
VAS		39.7 (25.9)
BDI		3.79 (2.58)
TDI		-5.41 (1.55)
OCD		0.280 (0.088)
Borg		3.62 (1.54)
Impairment of activities of daily living (LCADL)		54.1 (5.8)
Health related quality of life (SGRQ)		
Symptoms		83.1 (13.9)
Activities		87.9 (11.9)
Impacts		62.8 (16.2)
Total		73.8 (12.5)

Change during Exacerbation

Within breath X_{rs} and R_{rs} results for three representative subjects from the three study visits are shown in Figure 3. Qualitatively it can be seen that the three subjects show a larger proportional change in X_{rs} than R_{rs}. The changes in physiological variables during the exacerbation are shown in Table 2. Percentage change values were derived in different ways for the spirometry and oscillometry variables. As lung volumes and flows were typically reduced and reliable predicted values available, these were given as % change relative to the predicted values. Since oscillometry values were higher than normal during the exacerbation and predicted values less well known, the denominator for % change was the average of the values at the relevant visit. These results are also summarised in Figure 4. The changes between visits 2 and 3 are not shown in detail as they were smaller and generally not significant (with the exception of FEV_1, PEF, $X_{rs,insp}$, Paggiaro symptom score, TDI, Dyspnoea (VAS) and LCADL which were marginally significant). This time course of change is illustrated in Figure 5.

To obtain a measure of the "signal to noise" content or sensitivity index of the physiological measurements,[28] the changes between visits 1 and 3 are shown in Table 3 divided by the reproducibility or coefficient of variation of the measurement.[29] FEV_1, VC and IC were the more reliable measurements followed by the X_{rs} variables.

Table 2. Change in variables between visits for all patients. All data are mean ± SEM unless otherwise indicated. The statistical significance of paired changes was assessed using the Student paired t test. The statistical significance of % changes was assessed using the equivalent one sample test, with the null hypothesis being a mean change of zero.

			Visit 2 – Visit 1 n=37	Visit 3 – Visit 1 n=36
Spirometry				
VC	**L**		**0.297 ± 0.061**§	**0.354 ± 0.071**§
	% pred		**10.3 ± 1.8**§	**12.1 ± 2.3**§
FEV_1	**L**		**0.153 ± 0.046**‡	**0.274 ± 0.064**§
	% pred		**6.37 ± 1.71**‡	**11.4 ± 2.3**§
FEV_1/VC	**%**		0.200 ± 1.100	3.18 ± 1.47 †
PEF	**$L.s^{-1}$**		**0.455 ± 0.140**‡	**0.696 ± 0.142**§
	% pred		**6.80 ± 2.18**‡	**11.0 ± 2.2**§
IC	**L**		**0.241 ± 0.054**§	**0.295 ± 0.056**§
	% pred		**9.87 ± 1.98**§	**11.9 ± 2.3**§
Capillary earlobe blood gases				
P_aO_2	**kPa**		**0.85 ± 0.18**§	**1.18 ± 0.21**§
P_aCO_2	**kPa**		0.06 ± 0.13	0.02 ± 0.14
Breathing pattern				
Respiratory rate		**min^{-1}**	**-1.37 ± 0.65**†	**-1.57 ± 0.64**†
Tidal volume		**L**	-0.002 ± 0.029	0.008 ± 0.183

* $p<0.1$, † $p<0.05$, ‡ $p<0.005$, § $p<0.0005$.

Table 2. (Continued)…..

		Visit 2 – Visit 1 n=37	Visit 3 – Visit 1 n=36
Oscillometry			
R_{rs}	**kPa.s.L^{-1}**	-0.025 ± 0.020	-0.009 ± 0.024
	%	-3.60 ± 3.47	-0.95 ± 3.9
X_{rs}	**kPa.s.L^{-1}**	**0.132 ± 0.034§**	**0.143 ± 0.039‡**
	%	**27.9 ± 7.0§**	**35.2 ± 8.9§**
$R_{rs,insp}$	**kPa.s.L^{-1}**	-0.025 ± 0.015	-0.024 ± 0.019
	%	-4.97 ± 3.25	-3.91 ± 3.90
$X_{rs,insp}$	**kPa.s.L^{-1}**	**0.032 ± 0.011†**	**0.073 ± 0.017§**
	%	**13.0 ± 4.5†**	**27.4 ± 6.7§**
$R_{rs,exp}$	**kPa.s.L^{-1}**	-0.020 ± 0.027	0.006 ± 0.030
	%	-2.57 ± 4.09	1.25 ± 4.22
$X_{rs,exp}$	**kPa.s.L^{-1}**	**0.193 ± 0.050§**	**0.180 ± 0.054‡**
	%	**31.5 ± 7.8§**	**37.1 ± 10.0‡**
%FL	**%**	**-19.2 ± 6.1‡**	**-19.5 ± 7.0†**

* $p<0.1$, † $p<0.05$, ‡ $p<0.005$, § $p<0.0005$.

Table 2. (Continued)…..

	Visit 2 – Visit 1 n=37	Visit 3 – Visit 1 n=36
Symptom score		
VAS		
Sleep	**30.5 ± 8.1**‡	**23.5 ± 9.3**†
Wheeze	**17.7 ± 6.5**†	**22.6 ± 8.4**†
Mobility	**31.8 ± 6.5**§	**37.1 ± 7.6**§
Paggiaro	**-1.70 ± 0.54**‡	**-3.14 ± 0.62**§
Dyspnoea		
VAS	**16.9 ± 4.3**§	**27.0 ± 5.7**§
TDI	**1.92 ± 0.33**§	**3.39 ± 0.405**§
OCD	**0.068 ± 0.018**‡	**0.101 ± 0.027**‡
Borg	**-0.973 ± 0.205**§	**-1.15 ± 0.281**‡
Impairment of activities of daily living (LCADL)	**-7.24 ± 0.90**§	**-11.6 ± 1.3**§
SGRQ		
Symptoms		0.121 ± 2.41
Activities		**-4.76 ± 2.26**†
Impacts		**-9.88 ± 2.92**‡
Total		**-6.67 ± 1.96**‡

* p<0.1, † p<0.05, ‡ p<0.005, § p<0.0005.

Table 3. Sensitivity index of spirometry and oscillometry measurements. This analysis uses % change rather than % predicted values for spirometry in order to be comparable with the coefficient of variation.

		Change (Visit 3 – Visit 1)	Coefficient of variation (%)	Sensitivity Index
Spirometry				
VC	**% change**	15.5	7.2	2.15
FEV_1	**% change**	24.8	9.6	2.58
IC	**% change**	16.7	8.8	1.90
Oscillometry				
R_{rs}	**% change**	-0.95	12.2	0.08
X_{rs}	**% change**	35.2	24.1	1.46
$R_{rs,insp}$	**% change**	-3.91	14.0	0.28
$X_{rs,insp}$	**% change**	27.4	17.6	1.56
$R_{rs,exp}$	**% change**	1.25	13.2	0.09
$X_{rs,exp}$	**% change**	37.1	28.6	1.30
%FL	**change**	-19.5	13.3	1.47

Correlation Between Physiological Variables and Symptoms

Pearson correlation coefficients were calculated between changes in physiological variables and changes in symptoms or HRQOL and are shown in the online supplement available at http://www.thoraxjnl.com/supplemental. The strongest correlation was seen between changes in P_aO_2 and OCD score (r=0.594; p=0.0001). Of the spirometric variables, changes in FEV_1 showed the strongest associations with changes in symptoms, having significant correlations with changes in OCD (r=0.500; p=0.002), TDI (r=0.372; p=0.02) and LCADL score (r=0.499; p=0.002). By contrast changes in IC were only associated with changes in mobility (r=0.329; p=0.05). Changes in $X_{rs,insp}$ were widely associated with changes in symptoms, showing positive correlations with changes in OCD (r=0.430; p=0.01), TDI (r=0.458; p=0.009), LCADL (r=0.408; p=0.01) and mobility (r=0.493; p=0.003). Changes in $X_{rs,exp}$ showed fewer significant correlations. Both changes in $X_{rs,insp}$ and $X_{rs,exp}$ showed significant correlations with change in total SGRQ score (r=0.442, p=0.003 and r=0.428 , p=0.009).

DISCUSSION

This study has demonstrated that improvement following an exacerbation of COPD can be detected either objectively by physiological measurements such as spirometry, oscillometry or gas exchange or subjectively by the simpler strategem of following symptom scores or HRQOL (Table 2 and Figure 4). The majority of the improvement in all variables occurred within the first week of monitoring (Table 2 and Figure 5).

In the study subjects there was a uniformly significant improvement in symptoms, ADLs and improvement in SGRQ (with the exception of the Symptoms score) confirming subjective recovery from the exacerbation. All the spirometric variables (i.e. FEV_1, PEF, VC, IC) increased significantly with the exception of FEV_1/VC which is in line with findings elsewhere.[1][2][3][4] One difference found here was that the size of the change was very consistent in terms of % predicted ranging from 11.0% for PEF to 12.1% for VC. This diverges slightly from the results in the recent similar study by Stevenson et al. where the absolute value of IC was lower throughout and the change in IC was found to be larger (19% predicted).[14] Three factors which could account for these differences are the timing of the measurements, the baseline characteristics of the study populations and the technique used to measure IC. Firstly, the patients in this study had their initial measurements performed on average a day later than those in Stevenson's study by which time he had already documented an increase in IC approaching 0.1 L. Secondly, the subjects in Stevenson's study at baseline had lower BMI and higher P_aO_2 values than those in this study. Being underweight and relatively well oxygenated are two characteristics of the group of patients formerly called "pink puffers" whose other key characteristic is marked hyperinflation and hence a relatively reduced IC. Thirdly, IC was measured in this study during an expiratory VC manoeuvre whereas an inspiratory approach was used in Stevenson's study.

The subjects in this study showed a sizeable and significant increase in both $X_{rs,insp}$ and $X_{rs,exp}$ (27.4% and 37.1% respectively). As explained earlier, this can be interpreted physically as a decrease in both transpulmonary resistance and expiratory flow limitation respectively during the study period. By comparison there was no change in $R_{rs,insp}$ and $R_{rs,exp}$ (3.91% and 1.25% respectively). The study by Stevenson et al. is the only previous report of longitudinal changes of forced oscillometry variables during an exacerbation of COPD[14] and this showed a strikingly similar pattern of change to that seen here. They interpreted the lack of change in R_{rs} as implying that resistance does not improve during an exacerbation of COPD[14] but this inference can be contested. Firstly, in subjects with COPD, airway obstruction is present both during the exacerbation and after recovery. In this situation, the relationship between transpulmonary resistance and R_{rs} is weakened by the upper airway wall shunt[11] and changes in the former may not be reflected in the measured R_{rs} value. Secondly, a fall in resistance during recovery from an exacerbation is suggested by the significant rise in FEV_1 seen in this study. According to several models of flow limitation, maximal expiratory flow and hence FEV_1 is dictated by the

balance between thoracic elastic recoil and resistive pressure drop.[30] As recovery progressed in this study, the degree of hyperinflation in the subjects reduced and the magnitude of elastic recoil must have fallen. To produce an increase in FEV_1, there must have been a simultaneous and slightly greater fall in resistance.

To compare the relative ability of spirometry and oscillometry to detect improvement during an exacerbation of COPD, the sensitivity index of each variable was calculated by dividing the change in the variable by its coefficient of variation (Table 3). This effectively estimated the variable's signal to noise ratio. It can be seen that spirometry was the superior measurement in this analysis. The coefficient of variation of the X_{rs} results could be improved by increasing the amplitude of the 5 Hz forcing signal which would improve signal to noise ratio or by increasing the number of data points averaged in the calculation of one X_{rs} value (by either prolonging the duration of data collection or increasing the number of times the measurement is repeated).

To assess the ability of changes in physiological variables to predict changes in symptoms or HRQOL, the correlation coefficients between changes in these variables from visit 1 to visit 3 were calculated (shown in the online supplement available at http://www.thoraxjnl.com/supplemental). The broadest association with symptomatic improvement was found for changes in FEV_1, P_aO_2 and $X_{rs,insp}$. Only changes in the oscillometry variables ($X_{rs,insp}$ and $X_{rs,exp}$) were associated with changes in HRQOL. Conversely, the symptom scales most broadly associated with physiological improvement appeared to be the TDI score and the VAS for mobility. Changes in Borg score were not correlated with physiological improvement and changes in PEF were not associated with symptom or HRQOL changes. The strength of all significant associations was modest at best. If the conservative Bonferroni correction was applied to compensate for the multiple statistical comparisons made, then only the association between changes in PaO2 and changes in OCD score remained positive.

A surprising aspect of the correlation analysis was the relatively weak association of change in IC with symptomatic improvement. Recently it was shown that change in resting IC post-bronchodilator was the strongest predictor of subsequent improvement in exercise capacity.[31] Also Stevenson et al.[14] found that patients reporting less breathlessness at the time of discharge were those in whom IC improved most during recovery. One factor contributing to this difference was that the patients in this study showed a slightly different pattern of physiological abnormality at baseline and change during recovery. The patients here showed more of an obstructive picture (mean baseline FEV1: 0.96 L [43% predicted] compared with 1.03 L [47% predicted];[14] mean change in FEV1: 0.274 L [11.4% predicted] compared with 0.20 L[14]) and less hyperinflation (mean baseline IC: 1.70 L [77% predicted] compared with 1.37 L [62% predicted];[14] change in IC: 0.295L [11.9% predicted] compared with 0.42 L [19% predicted][14]). When combined with the inferior reproducibility (in absolute terms) of IC measurements, the biological noise in the measurements may have masked the association between change in IC and change in symptoms or HRQOL in this study.

Several difficulties were encountered in performing this study. Firstly, unless pre-exacerbation data are available, there are no precise objective criteria for establishing

when a patient has reached a stable state post-exacerbation. This was defined pragmatically here as a time point at least six weeks after visit 1 with the patient at home in what they deemed a stable condition and on normal medication. Secondly, it was difficult to achieve complete follow up with the type of subjects in this study due to chronic severe symptoms and the tendency to relapse. For clinical reasons, there was some variability in the exact time point at which the patients were assessed but the principle of assessing them at the beginning, early in recovery and then when largely back to stable state was achieved with reasonable success.

In conclusion, the physiological changes seen during recovery from an exacerbation of COPD comprised both an improvement in operating lung volumes (shown by IC) and a reduction in airway obstruction (assessed by FEV_1 and X_{rs}). Forced oscillometry is potentially an attractive and simple test to perform in these breathless patients because it is a passive manoeuvre requiring only tidal breathing. Spirometry does have superior signal to noise behaviour but by comparison with oscillometry is a maximal test which can be unpleasant to perform and leads to increased symptoms post-procedure. Changes in $X_{rs,insp}$ and $X_{rs,exp}$ were easily detected during an exacerbation in COPD subjects, were widely associated with changes in symptom and HRQOL scores and could represent useful objective measurements for documenting recovery from an exacerbation. By contrast changes in $R_{rs,insp}$ and $R_{rs,exp}$ were small in COPD subjects and not useful in this context.

Figure Legends

Figure 1. Study design showing order of tests
Figure 2. Flowchart showing subject recruitment
Figure 3. Within breath R_{rs} and X_{rs} values from three subjects (A, B and C) demonstrating the typical patterns of change between visits 1 to 3. The three subjects show a larger proportional change in X_{rs} than R_{rs}. Subject A experienced most improvement between study visits 2 and 3 whereas subject B changed most between visits 1 and 2. Subject C also showed improvement in both $X_{rs,insp}$ and $X_{rs,exp}$ but the continued expiratory fall in $X_{rs,exp}$ suggested persistent flow limitation during tidal breathing throughout the study.
Figure 4. Comparison of the magnitude of the mean percentage changes in spirometry and oscillometry parameters between visit 1 and visit 3. Spirometry values are given as change in % predicted. % changes in oscillometry parameters were calculated by averaging the results from the first and last visits and using this as the denominator. Error bars show SEM. ‡ $p<0.005$, § $p<0.0005$, *NS* non-significant
Figure 5. Time course of recovery of physiological variables. (A) Volumes and flows (B) X_{rs} (C) %FL. Values are mean change relative to visit 1. Error bars show SEM.

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Competing Interests
The authors have no competing interests to declare.

Ethical Approval

Ethical approval for this study was obtained from the GRI Local Research & Ethics Committee (Glasgow, UK).

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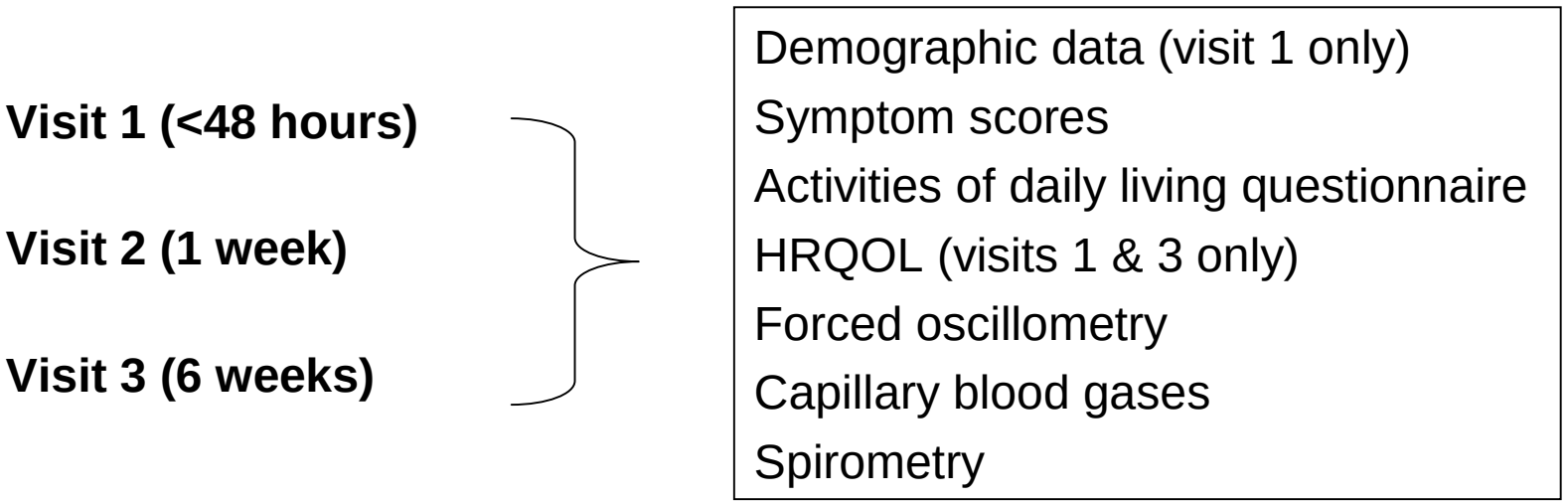

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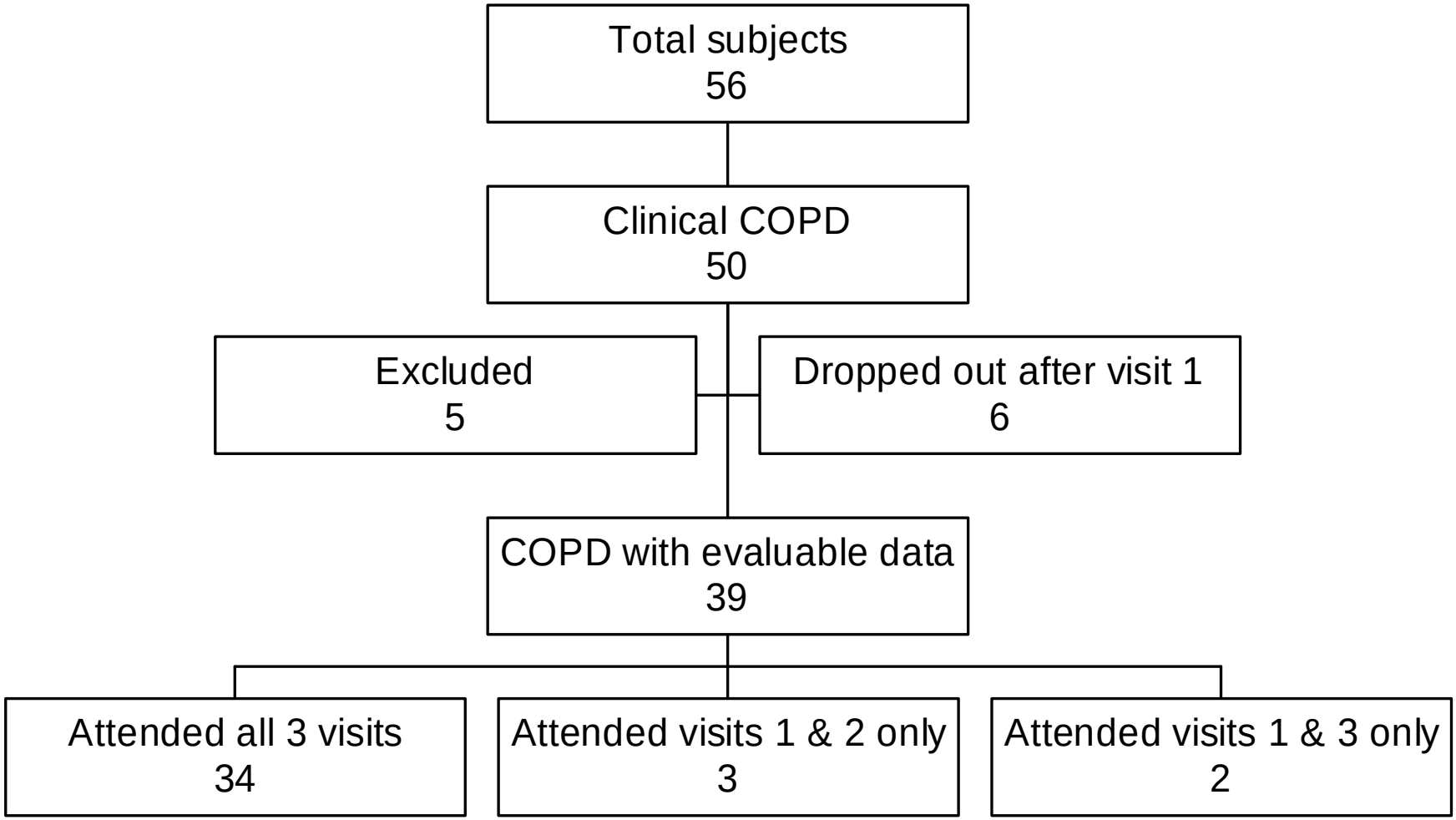

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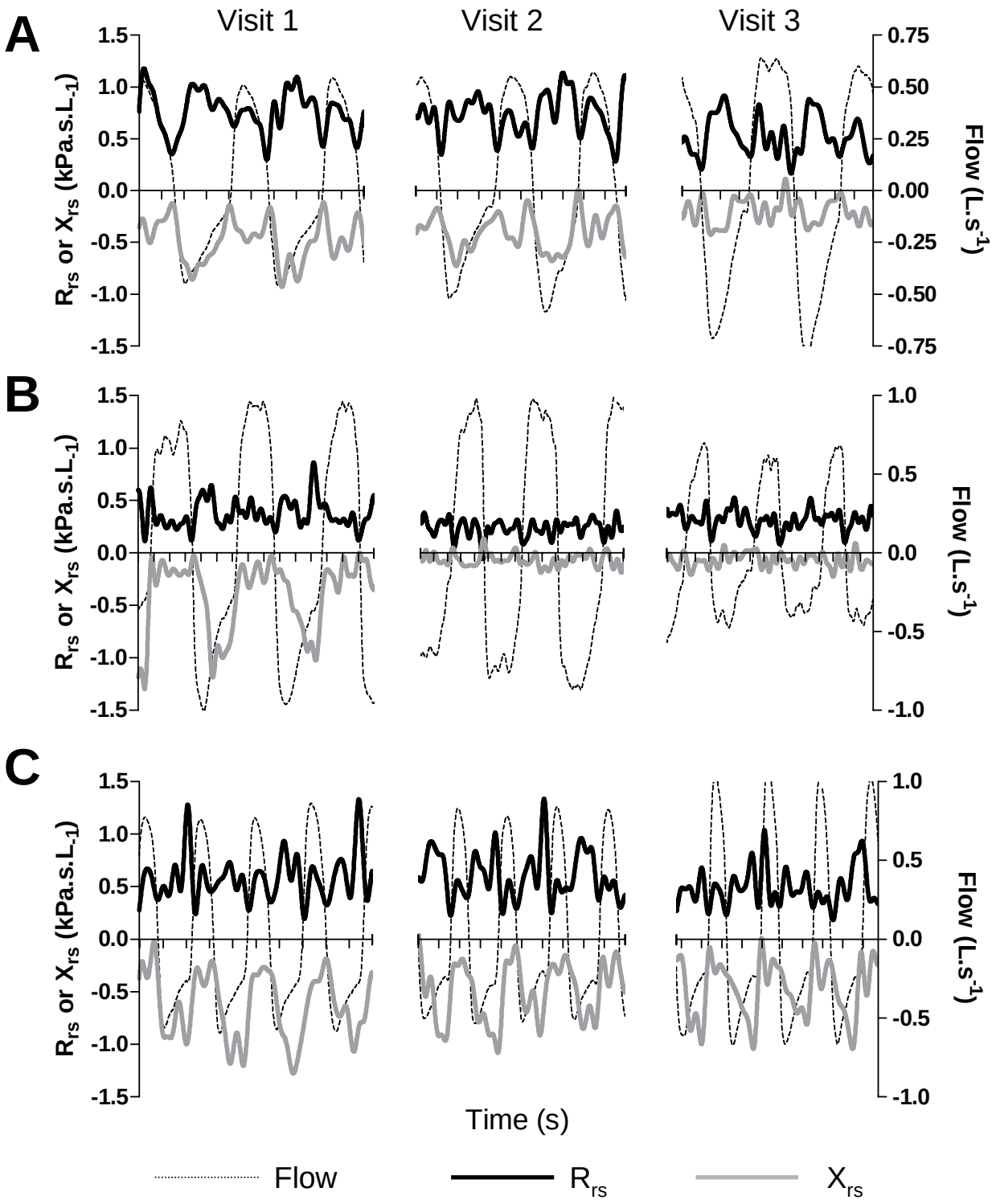

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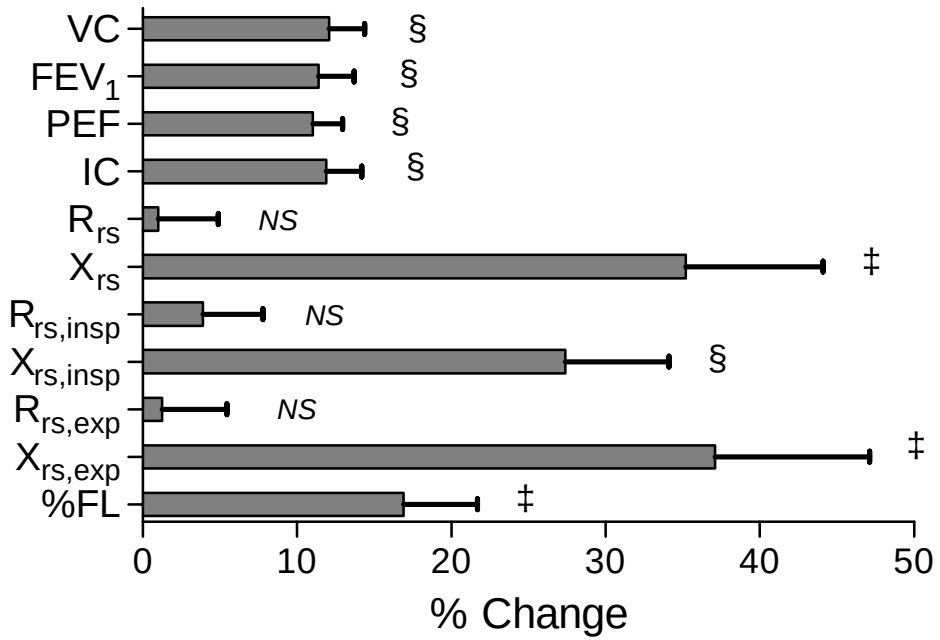

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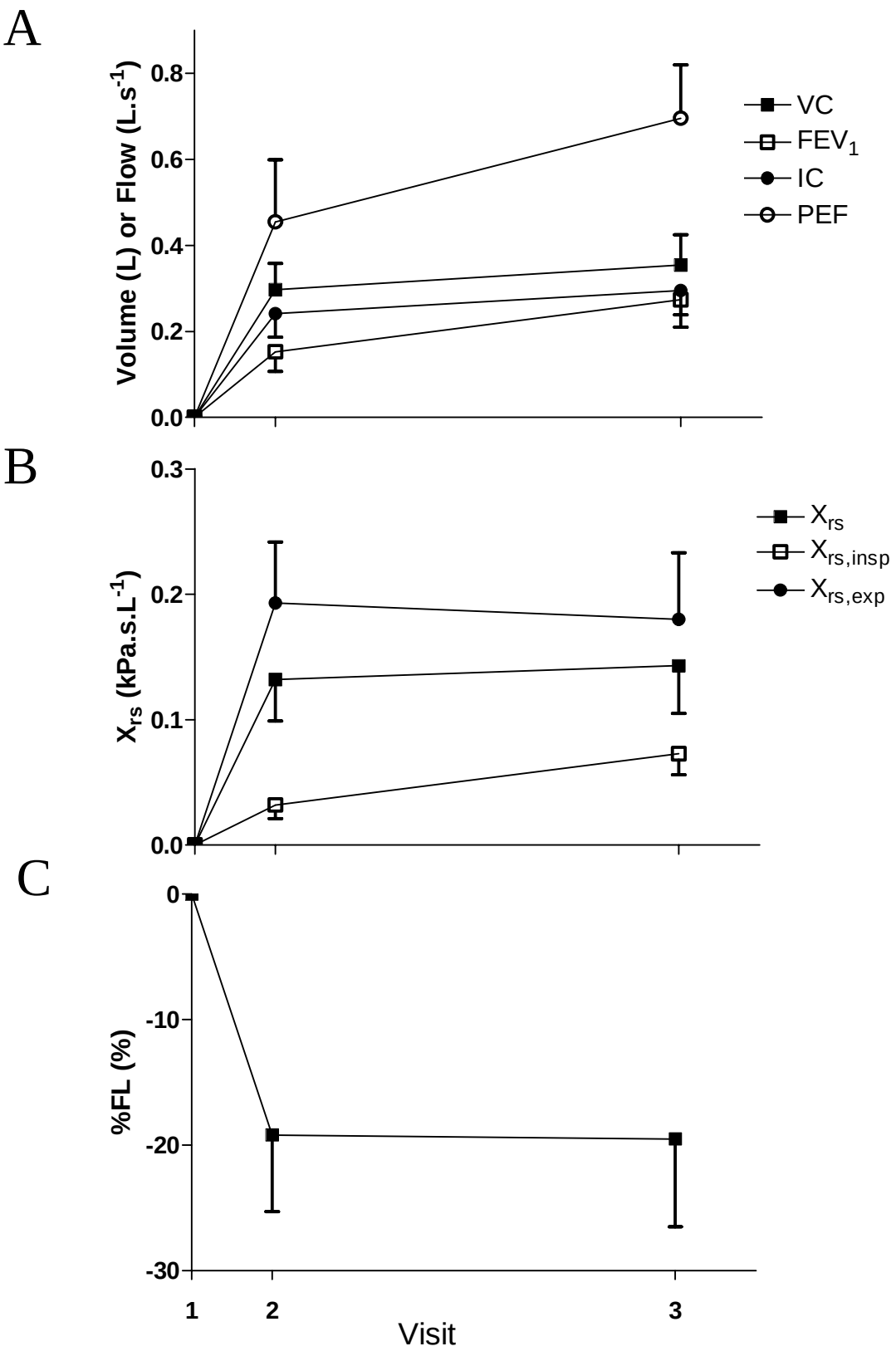

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