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ORIGINAL ARTICLE

Comparison of two methods of determining lung de-recruitment, using the forced oscillation technique

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Abstract

Airway closure has proved to be important in a number of respiratory diseases and may be the primary functional defect in asthma. A surrogate measure of closing volume can be identified using the forced oscillation technique (FOT), by performing a deflation maneuver and examining the resultant reactance (Xrs) lung volume relationship. This study aims to determine if a slow vital capacity maneuver can be used instead of this deflation maneuver and compare it to existing more complex techniques. Three subject groups were included in the study; healthy ($n = 29$), asthmatic ($n = 18$), and COPD ($n = 10$) for a total of 57 subjects. Reactance lung volume curves were generated via FOT recordings during two different breathing manoeuvres (both pre and post bronchodilator). The correlation and agreement between surrogate closing volume ($\mathrm{Vol}_{\mathrm{crit}}$) and reactance ($\mathrm{Xrs}_{\mathrm{crit}}$) at this volume was analysed. The changes in $\mathrm{Vol}_{\mathrm{crit}}$ and $\mathrm{Xrs}_{\mathrm{crit}}$ pre and post bronchodilator were also analysed. Across all three subject groups, the two different measures of $\mathrm{Vol}_{\mathrm{crit}}$ were shown to be statistically equivalent ($p > 0.05$) and demonstrated a strong fit to the data ($R^2 = 0.49$, 0.78, 0.59, for asthmatic, COPD and healthy subject groups, respectively). A bias was evident between the two measurements of $\mathrm{Xrs}_{\mathrm{crit}}$ with statistically different means ($p < 0.05$). However, the two measurements of $\mathrm{Xrs}_{\mathrm{crit}}$ displayed the same trends. In conclusion, we have developed an alternative technique for measuring airway closure from FOT recordings. The technique delivers equivalent and possibly more sensitive results to previous methods while being simple and easily performed by the patient.

Keywords Forced oscillation technique · Lung de-recruitment · Reactance · Airway closure

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This study demonstrates a new and improved technique for identifying closing volume via FOT measurements. The technique delivers equivalent and possibly more sensitive results to previous methods while being simple and easy to perform for the patient.

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Abbreviations

ACQ6	Asthma control questionnaire-6
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 s
FOT	Forced oscillation technique
FVC	Forced vital capacity
RV	Residual volume
SVC	Slow vital capacity
TLC	Total lung capacity
$\mathrm{Vol}_{\mathrm{crit}}$	Critical volume
Xrs	Reactance
$\mathrm{Xrs}_{\mathrm{crit}}$	Critical reactance

Introduction

Airway closure has proved to be important in a number of respiratory diseases including asthma (Wagner et al. 1998, 2005; Veen et al. 2000), COPD (O'Donnell et al. 2004) and in acute lung injury (Cheng et al. 1995; Rimensberger et al. 1999; Martin-Lefevre et al. 2001). These studies suggest that lung de-recruitment begins in the peripheral airways (Hughes et al. 1970). Both forced oscillation technique (FOT) (Kelly et al. 2012) studies and imaging studies (Samee et al. 2003; de Lange et al. 2006a, b) have demonstrated that airway closure in patients with asthma is increased when compared to healthy subjects and is most likely a significant contributor to the reduction in FEV_1.

There are no tests to assess airway closure that are used routinely in the clinical setting. Common respiratory tests that offer measurements of gas trapping such as plethysmography (Standardization of spirometry—1987 update. Statement of the American Thoracic Society 1987) or multiple breath gas washout (Downie et al. 2013), can help identify the presence of ventilation inhomogeneity and hence indirectly measure airway closure. However, these tests provide no detail at what lung volume airway closure occurs. A number of single breath gas washout tests have been developed to identify closing volume (Anthonisen et al. 1970; Dollfuss et al. 1967; Milic-Emili et al. 1966) via the identification of phase-IV slopes from slow vital capacity (SVC) maneuvers but have not been utilised as a routine clinical tool.

Recent studies have demonstrated that de-recruitment can be examined via FOT. Dellaca et al., demonstrated that lung compliance derived from reactance Xrs (Dellaca et al. 2009) correlates well with the percentage of ventilated lung obtained via computed tomography. Kelly et al. (2012, 2013) demonstrated that a deflation maneuver can be used to generate reactance (Xrs) lung volume relationship. A sharp reduction in Xrs evident on the Xrs lung volume relationship is associated with lung de-recruitment and a surrogate measure of airway closure (critical volume) (Kelly et al. 2012, 2013). This technique requires the subject to perform a deflation maneuver, using multiple stepped breaths (Fig. 1a), beginning at total lung capacity (TLC) and with each breath reducing the subjects lung volume a little more than the last breath, until the subject reaches residual volume (RV). This breathing pattern was first developed to enable the calculation of FOT impedance at instances of zero flow (the end of inspiration and expiration) to minimise the effects of flow on impedance (Marchal et al. 1999; Brown et al. 2007). In the authors' experience, this deflation maneuver can be difficult for some subjects to complete successfully. To generate a useful Xrs lung volume curve, multiple breaths between functional residual capacity (FRC) and RV are essential. In particular, subjects with airflow obstruction experience difficulty performing these breaths between FRC and RV.

This study aims to determine if a slow vital capacity maneuver (SVC) (a slow inhalation to TLC followed by a slow exhalation to RV) during a FOT test can be used to identify the critical volume. We also test the hypothesis that the SVC maneuver will deliver comparable results to alternative, previously described methods, of identifying a surrogate measure closing volume from FOT.

Methods

Three subject groups were included in the study; healthy ($n = 29$), asthmatic ($n = 18$), and COPD ($n = 10$) for a total of 57 subjects. The three patient groups were chosen as each condition has a different effect on lung mechanics. Each subject provided written informed consent and the studies were either approved by the Ethics Committee of the Alfred Hospital (Victoria, Australia) or Oxford C REC The healthy subjects had no history of respiratory disease and spirometry was within normal limits. The subjects with asthma were a mix of well controlled and poorly controlled subjects in line with current guidelines (National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR3): Guidelines for the

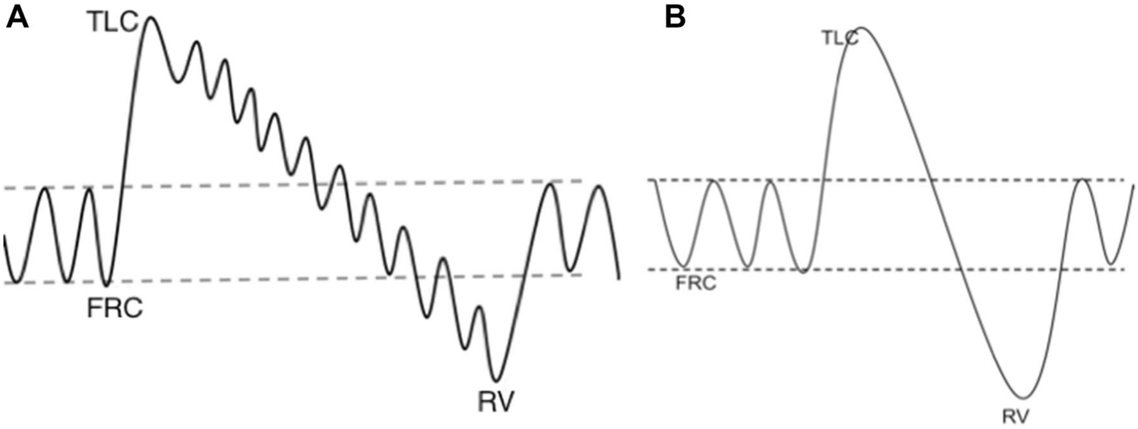

Fig. 1 Examples of the breathing maneuvers used to generate the reactance lung volume relationship. **a** A single deflation maneuver. Samples of Xrs and lung volume are taken at the peak and troughs in volume trace. **b** Slow vital capacity maneuver. Samples of Xrs and lung volume are taken every 0.1 s during the maneuver

Diagnosis and Management of Asthma 2007) and have been used in prior publications (Kelly et al. 2012, 2013). Mild and moderate COPD subjects as defined by Global Initiative for Obstructive Lung Disease guidelines were also included (Miravitlles et al. 2016).

Each subject had estimates of total lung capacity from body plethysmography followed by surrogate measures of airway closure using FOT. For the FOT measurements, airway closure was estimated using two different breathing maneuvers, the previously published deflation maneuver (Fig. 1a) and the slow vital capacity (Fig. 1b) maneuver. All measurements were performed at baseline and post administration of short acting beta2-agonist (salbutamol) via a spacer. Asthmatic subjects were administered 300 µg of salbutamol while COPD and healthy subjects were administered 400 µg. Before testing each asthmatic and COPD subject withheld both short and long acting bronchodilator medications. This resulted in a total of 228 paired FOT recordings. The commercial TremoFlo™ FOT device from Thorasys (Canada) was used for the healthy and COPD subjects, while an in house custom FOT device described previously (Salome et al. 2003) was used for the subjects with asthma. As Xrs within the frequency range 5–8 Hz has been shown to be highly effective at showing changes in tissue mechanics (Kaczka et al. 1999; Lutchen and Gillis 1997), all subjects had Xrs at 6 Hz recorded for examination.

FOT data processing

Custom analysis software written in Matlab (MathWorks 2015b) was used to examine the FOT data, generate Xrs lung volume relationships, and determine $\mathrm{Vol}_{\mathrm{crit}}$ and $\mathrm{Xrs}_{\mathrm{crit}}$. FOT impedance was calculated from the raw pressure and flow signals. To isolate the FOT signals and reduce noise while maintaining a higher time resolution, a band pass filter with a bandwidth of 0.2 Hz was applied to both the pressure and flow signals using a zero-phase method, processing the data in both forward and reverse directions (Gustafsson 1996; Oppenheim et al. 1999). A window of 64 samples was selected to conduct the fast Fourier transform (Frigo and Johnson 2005) of the pressure and flow signals. Impedance was then calculated using the auto- and cross-spectra of pressure and flow (Bates et al. 2011; Michaelson et al. 1975).

Lung volume reactance relationship

In this study, a surrogate measure of closing volume is established by examining the relationship between Xrs and lung volume as a percentage of total lung capacity (Fig. 2). In this relationship, the critical volume ($\mathrm{Vol}_{\mathrm{crit}}$) was defined as the percentage lung volume at which a rapid decrease in Xrs associated with lung de-recruitment begins (Kelly et al. 2012, 2013). The Xrs of the $\mathrm{Vol}_{\mathrm{crit}}$ point was labelled as the critical reactance ($\mathrm{Xrs}_{\mathrm{crit}}$). The point where $\mathrm{Vol}_{\mathrm{crit}}$ and $\mathrm{Xrs}_{\mathrm{crit}}$ occurs is determined using breakpoint analysis (Stuart-Andrews et al. 2012; Kelly et al. 2012). Briefly, this method uses the intersection of two least squares regression lines to identify the point where the sudden reduction in Xrs begins (Fig. 2). The algorithm finds this breakpoint by splitting the lung volume reactance relationship into two segments of different sizes (n_1 and n_2). A separate regression line is calculated through each segment and the coefficient of determination (R^2) is calculated. On the first iteration $n_1 = 3$ and n_2 is data from all the remaining lung volume. The regression process is then repeated by increasing n_1 by one and decreasing n_2 by one until $n_2 = 3$. The iteration that obtained the highest R^2 value is used to identify the breakpoint. $\mathrm{Vol}_{\mathrm{crit}}$ and $\mathrm{Xrs}_{\mathrm{crit}}$ mark the breakpoint (Fig. 3b) on the Xrs lung volume curve where lung de-recruitment begins.

Deflation analysis

A breathing protocol first developed by Brown et al. (2007) and then modified by Kelly et al. (2012) was used to establish a full Xrs, lung volume relationship. This relationship was established using a specific breathing protocol performed during FOT testing (Fig. 1a). The protocol requires the subject to breath steadily with a normal tidal volume. Once a steady breathing pattern is established, a large breath up to total lung capacity (TLC)

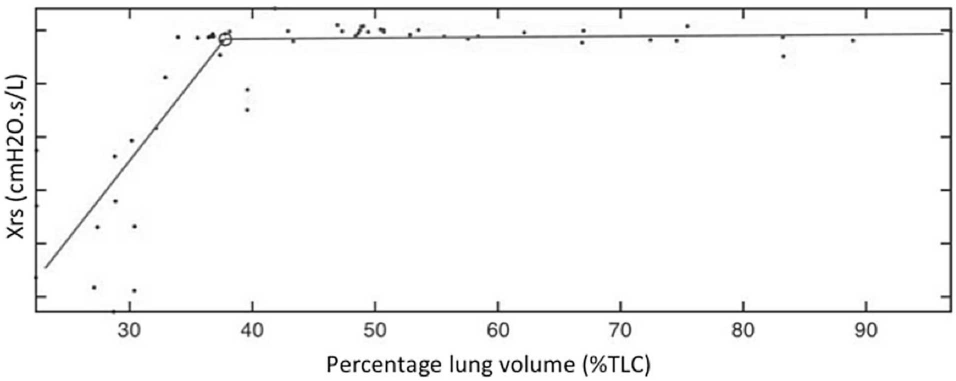

Fig. 2 Example of the reactance lung volume relationship generated from the deflation maneuver. Data is from a control subject. Break point analysis is used to determine the beginning of lung de-recruitment. The circle marks the break point and $\mathrm{Vol}_{\mathrm{crit}}$ is the percentage lung volume and $\mathrm{Xrs}_{\mathrm{crit}}$ is the reactance at this point. The two solid lines are the least square regression lines used to calculate the breakpoint

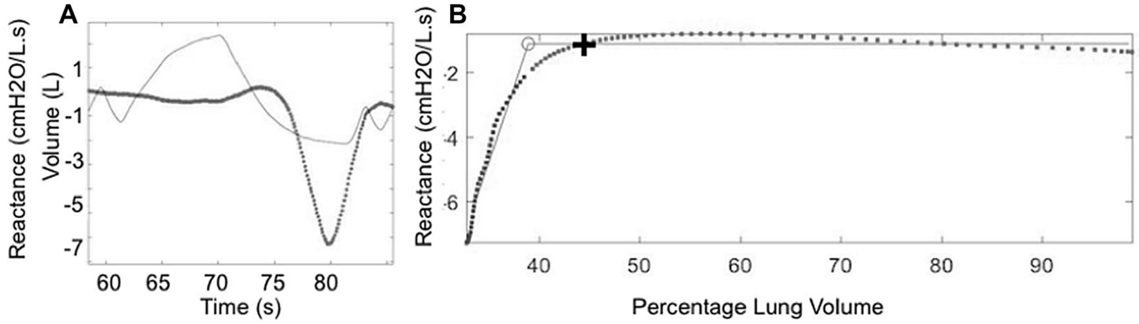

Fig. 3 Example of the SVC maneuver converted into the reactance lung volume relationship. Data are from a control subject. **a** The time course data during the SVC maneuver. The solid grey line is the volume and the black dots is the Xrs recorded every 0.1 s. **b** The reactance lung volume relationship generated from the SVC maneuver in part **a**. The reduction in reactance with closing volume can clearly be seen. The circle denotes the break point, where $\mathrm{Vol_{crit}}$ is taken. $\mathrm{Xrs_{crit}}$ marked by the cross. The two solid lines are the least square regression lines used to calculate the breakpoint

is taken and then with each subsequent exhaled breath, the subject breaths out a little further reducing their lung volume. The reduction of lung volume with each breath is continued until the subject reaches residual volume (RV) and the subject then resumes normal tidal breathing. The deflation maneuver is repeated up to 3 times. The Xrs lung volume relationship is determined by plotting each Xrs and volume point at the end of inhalation and exhalation (approximate zero flow) from each maneuver.

SVC analysis

To examine Xrs during an SVC maneuver, a continuous discrete time Xrs signal was generated by calculating Xrs every 0.1 of a second. Xrs was plotted against lung volume continuously instead of only at the end of inhalation or exhalation as done in the deflation maneuver described previously. An operator manually selected the beginning and end of the SVC maneuver by examining the volume trace. Only tests that had an SVC maneuver longer than 8 s and satisfied ATS/ERS criteria for a SVC maneuver (Miller et al. 2005; Wanger et al. 2005) were included in the study. The discrete time Xrs signal was then plotted against percentage of total lung volume, based on body plethysmography, and changes that occurred in Xrs during the SVC maneuver could be observed. Breakpoint analysis (Kelly et al. 2012, 2013; Stuart-Andrews et al. 2012) using the two least squares regression lines was also applied to the SVC, Xrs and percentage lung volume relationship, to determine the $\mathrm{Vol_{crit}}$ and $\mathrm{Xrs_{crit}}$. $\mathrm{Vol_{crit}}$ was the percentage lung volume of the breakpoint. The $\mathrm{Xrs_{crit}}$ was deemed to be the point where the upper (second) regression line intercepted the Xrs lung volume curve (Fig. 3).

Statistical analysis

The SVC maneuver was performed before the deflation maneuver with 30 s of tidal breathing between manuevers. This enabled each SVC maneuver to be paired with a deflation maneuver. Each subject performed two paired SVC and deflation maneuvers pre and post bronchodilator, resulting in four paired maneuvers per subject.

To compare the two methods of identifying critical volume, four different statistical tests were applied: (1) paired student *t* test, (2) intra-class correlation coefficient to test agreement between two variables, (3) least squares regression analysis and (4) Bland Altman (1986) plot analysis. The statistical tests were applied using Matlab (MathWorks 2015b). Each of the tests was applied to each subject group separately to identify any differences that may occur in different subject groups.

The ability of each method to show changes in $\mathrm{Vol_{crit}}$ pre and post bronchodilator, for each subject group was also compared using each of the statistical tests.

Results

The anthropometric measurements and pulmonary function results are displayed in Table 1. The only difference in anthropometric measurements between disease and healthy groups was age (assessed via an unpaired student *t* test). Both the asthmatic and COPD groups displayed airflow obstruction as their FEV1/FVC ratio was below the lower limit of normal and was only partially reversed following bronchodilator.

Table 1 Subject demographics and lung function

	Asthma	COPD	Healthy
Number of subjects	18	10	29
Gender male/female	11/7	6/4	14/15
Age (years)	54 ± 15.6*	71 ± 6.6*	63 ± 12.5
Height (cm)	171.1 ± 10.4	172 ± 6	170.7 ± 9.8
BMI (kg/m^2)	26.9 ± 7.0	29.9 ± 3.4	27.7 ± 6.2
FEV1% pred			
Pre BD	66.1 ± 14.9**	72.21 ± 10.9**	100.7 ± 12.1
Post BD	69.7 ± 13.8**	74.9 ± 10.6**	104.2 ± 11.5
FVC % pred			
Pre BD	91.6 ± 15.1**	99 ± 12.3	101.6 ± 7.6
Post BD	91.8 ± 13.7**	102.6 ± 13.6	101.7 ± 8.1
FEV1/FVC			
Pre BD	55.6 ± 14.6**	55.9 ± 10.4**	76.8 ± 11.2
Post BD	59.4 ± 13.2**	56.3 ± 9.5**	79.4 ± 10.8
FRC % pred			
Pre BD	114.2 ± 21.9**	103.6 ± 23.8*	91.4 ± 18.1
Post BD	108.2 ± 21.5**	98.9 ± 19.8	89.3 ± 19.5
TLC % pred			
Pre BD	115.4 ± 14.4**	99.3 ± 15.7	95.7 ± 13.4
Post BD	115.3 ± 13.8**	99.3 ± 15.1	96.4 ± 14.5

± Denotes the standard deviation

Predicted values were obtained from (Hankinson et al. 1999; Crapo et al. 1982)

FEV1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *FRC* functional residual capacity, *TLC* total lung capacity

*$p < 0.05$ and **$p < 0.01$ significant difference between disease and healthy subject groups using *t* test

Critical volume

Table 2 shows the statistical comparison of Vol$_{crit}$ identified by the two different breathing maneuvers. There was no statistical difference between Vol$_{crit}$ measured by either maneuver for each of the asthma, COPD and healthy groups. The intraclass correlation coefficients for all three subject groups (asthma = 0.69, healthy = 0.7 and COPD = 0.89) confirm that both measures for Vol$_{crit}$ are in agreement.

Regression analysis shows a strong positive correlation between Vol$_{crit}$ measure by the SVC and deflation maneuver for each of the subject groups (Fig. 4). The R^2 values from all of the subject groups (Table 2) demonstrate that the least squares model fits the data well and the *p* values from the *f* test show that the model is statistically significant.

The Bland Altman plots (Fig. 5) show that the there is no significant bias in any of the subject groups.

Critical reactance

There was a statistical difference in mean values of Xrs$_{crit}$ between results measured by the two maneuvers for all subjects and the individual disease groups (Table 1). In addition the intra-class correlation coefficients were fair to poor overall.

The least squares regression analysis demonstrates (Fig. 6) a correlation between the two methods of deriving Xrs$_{crit}$. The R^2 values (Table 2) for the asthmatic, COPD and healthy subjects were 0.2, 0.18 and 0.39, respectively, showing the regression model loosely fitted the data. The *p* values from the *f* test show that the model is statistically significant in all groups.

The Bland Altman plots of Xrs$_{crit}$ for each subject group (Fig. 7) shows that there is proportional bias in each group.

Pre and post bronchodilator comparison

Subjects with asthma had statistically significant changes ($p < 0.01$) in Vol$_{crit}$ pre and post bronchodilator derived from both of the breathing protocols. The COPD group had a significant change ($p < 0.05$) in SVC derived Vol$_{crit}$ but not in the deflation maneuver derived Vol$_{crit}$. The healthy group rejected the null hypothesis ($p > 0.05$) in both the SVC and deflation maneuver protocol (Table 3).

In all groups the *t* test rejected the null hypothesis ($p > 0.05$) that pre and post bronchodilation Xrs$_{crit}$ was statistically different.

There was no statistical difference ($p > 0.05$) in the change in Vol$_{crit}$ pre and post bronchodilator between the two breathing protocols in each of the subject groups (Table 4).

Table 2 Assessment of correlation and agreement between results derived from the deflation maneuver and the SVC maneuver

	Critical volume			Critical reactance		
	Asthma	COPD	Healthy	Asthma	COPD	Healthy
t test (*p*)	0.25	0.42	0.79	< 0.001	0.047	< 0.001
ICC	0.69	0.87	0.7	0.29	0.39	0.48
R^2	0.49	0.78	0.59	0.2	0.18	0.39
f test (*p*)	< 0.0001	< 0.0001	< 0.0001	< 0.01	< 0.0001	< 0.0001

The *p* value is derived via a paired *t* test. ICC is the intra-class correlation coefficient, and the R^2 values and the *f* test *p* values are derived during least squares regression

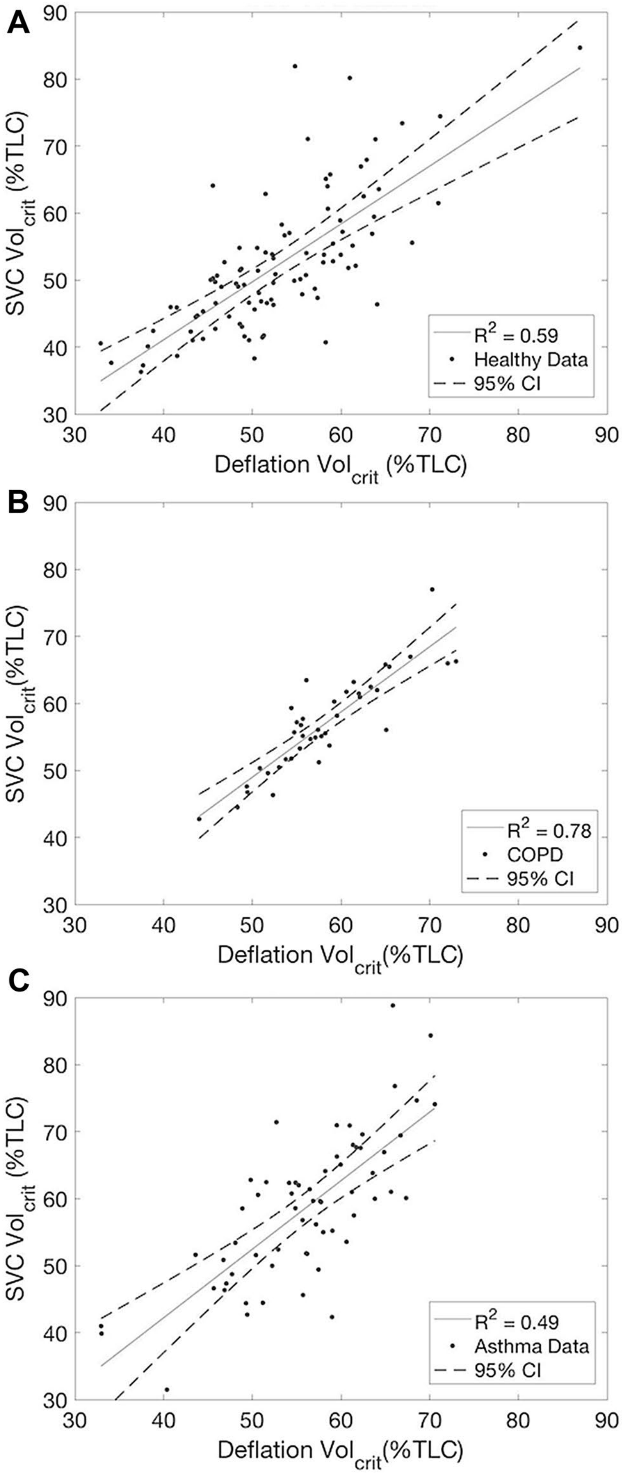

Fig. 4 Least squares regression analysis between Vol_{crit} obtained from the SVC and deflation maneuvers. Two paired maneuvers were completed and compared, pre and post bronchodilator per subject. %TLC is defined as percentage total lung capacity. The solid line is the regression fit of the data. **a** Analysis of the healthy subject group ($n = 29$ for a total of 116 paired maneuvers). **b** Analysis of the COPD subject group ($n = 10$ for a total of 40 paired maneuvers). **c** Analysis of the asthmatic subject group ($n = 18$ for a total of 72 paired maneuvers)

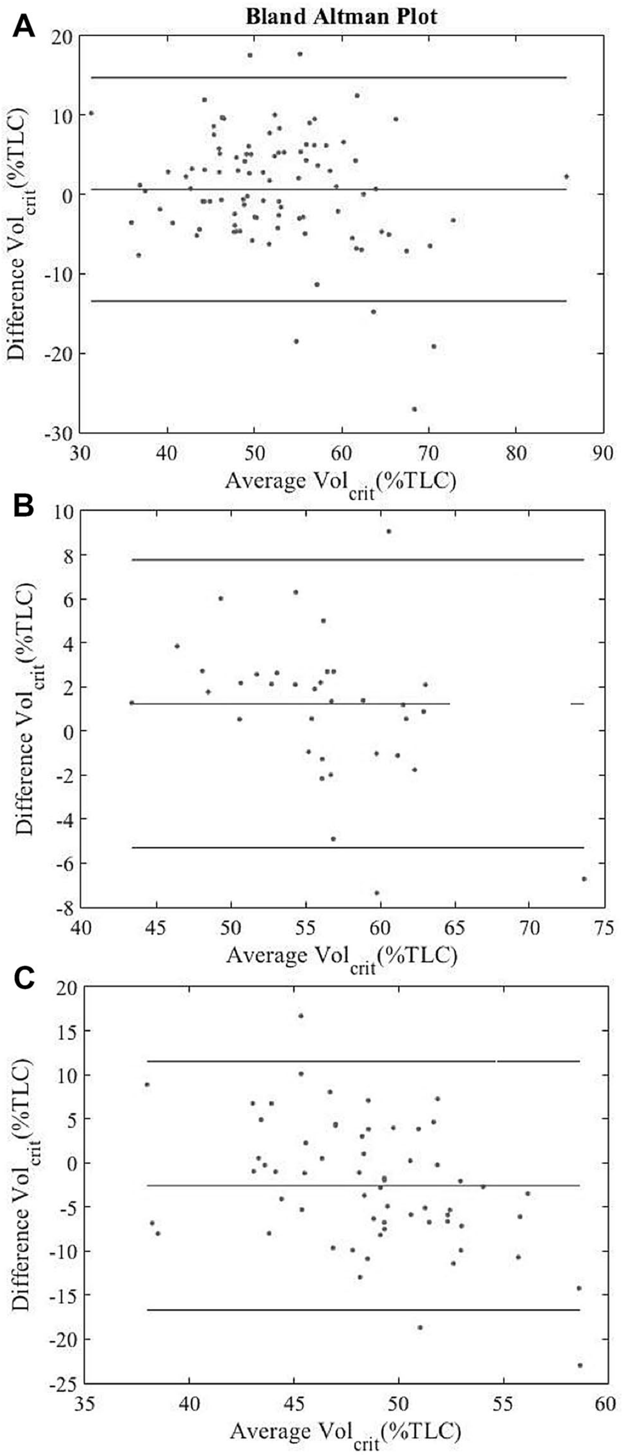

Fig. 5 Bland Altman analysis for Vol_{crit} obtained from the SVC maneuver and the deflation maneuver. The outer lines represent the limits of agreement and the center line is the mean. %TLC is defined as percentage total lung capacity. Two paired maneuvers were completed and compared, pre and post bronchodilator per subject. **a** Analysis of the healthy subject group ($n = 29$ for a total of 116 paired maneuvers). **b** Analysis of the COPD subject group ($n = 10$ for a total of 40 paired maneuvers). **c** Analysis of the asthmatic subject group ($n = 18$ for a total of 72 paired maneuvers)

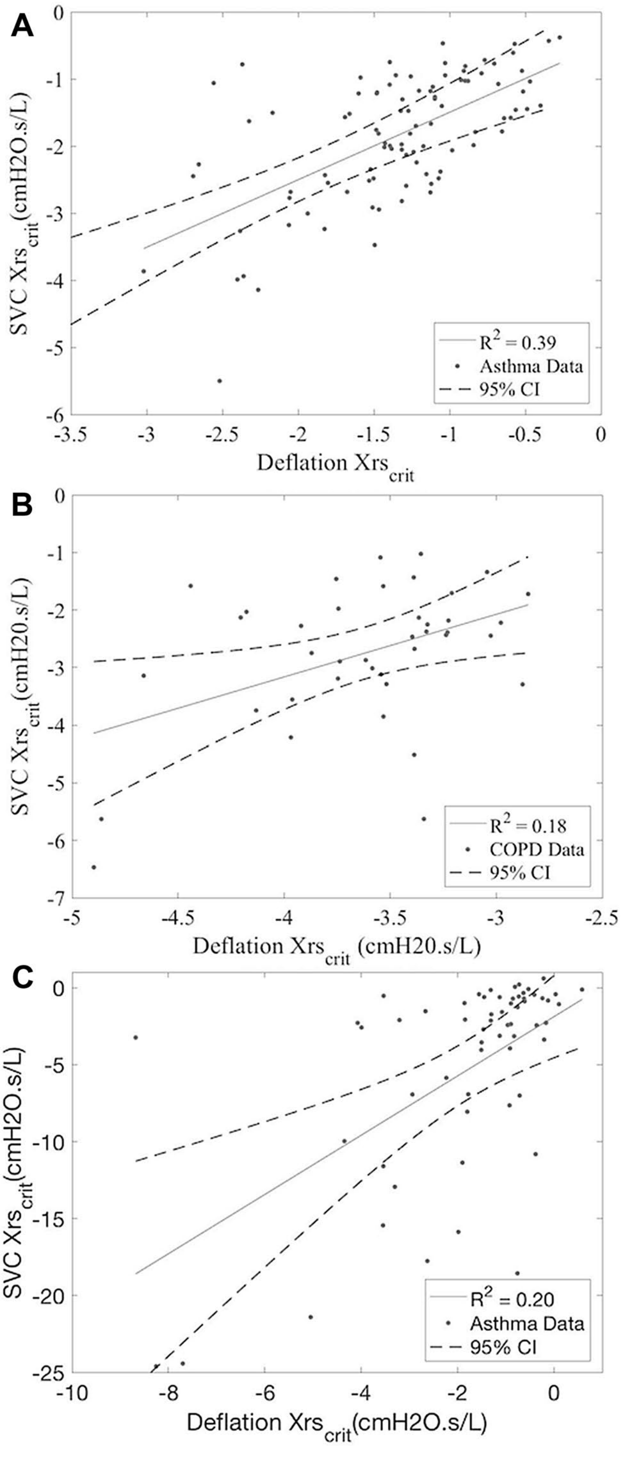

Fig. 6 Least squares regression analysis between $\mathrm{Xrs}_{\mathrm{crit}}$ obtained from the SVC and deflation maneuvers. Two paired maneuvers were completed and compared, pre and post bronchodilator per subject. **a** Analysis of the healthy subject group ($n=29$ for a total of 116 paired maneuvers). **b** Analysis of the COPD subject group ($n=10$ for a total of 40 paired maneuvers). **c** Analysis of the asthmatic subject group ($n=18$ for a total of 72 paired maneuvers)

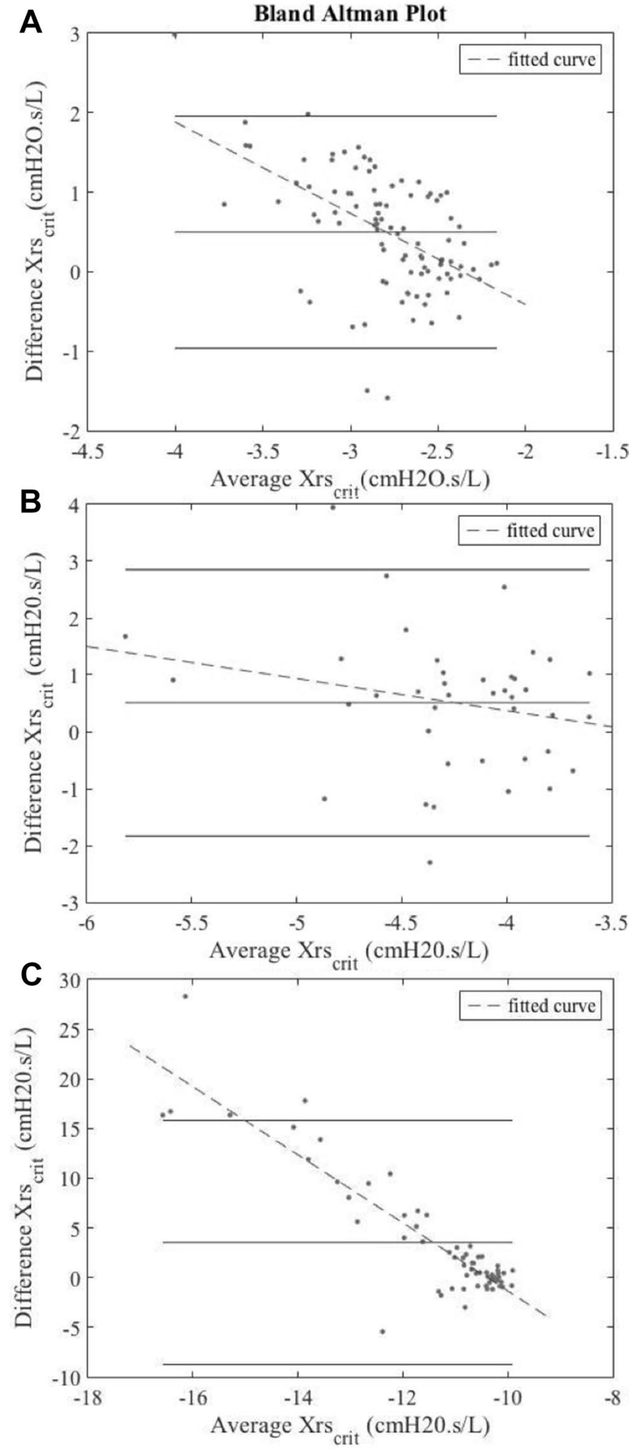

Fig. 7 Bland Altman analysis of $\mathrm{Xrs}_{\mathrm{crit}}$ obtained from the SVC and deflation maneuvers. The outer lines represent the limits of agreement and the center line is the mean. Two paired maneuvers were completed and compared, pre and post bronchodilator per subject. **a** Analysis of the healthy subject group ($n=29$ for a total of 116 paired maneuvers). **b** Analysis of the COPD subject group ($n=10$ for a total of 40 paired maneuvers). **c** Analysis of the asthmatic subject group ($n=18$ for a total of 72 paired maneuvers). *F* test *p* values for all. Log Bland Altman analysis of log $\mathrm{Xrs}_{\mathrm{crit}}$ has now been removed

Table 3 $\mathrm{Vol_{crit}}$ and $\mathrm{Xrs_{crit}}$ from the deflation maneuver and SVC maneuver pre and post bronchodilator

	Critical volume (% TLC)			Critical reactance ($\mathrm{cmH_2O/Ls}$)		
	Asthma	COPD	Healthy	Asthma	COPD	Healthy
(a) Deflation						
Pre BD	57 ± 7.3**	59.6 ± 6.5**	49.9 ± 5.6	− 2 ± 1.1*	− 2.5 ± 1.8*	− 1.33 ± 1.2
Post BD	49 ± 7.1	56.6 ± 7.2*	49.1 ± 5.4	− 1.33 ± 1.9	− 2 ± 1.6	− 1.18 ± 1.0
t test *p*	< 0.01	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
(b) SVC						
Pre BD	64 ± 9.2**	63.9 ± 6.8**	54.2 ± 6.1	− 6 ± 3.2**	− 2.8 ± 2.1*	− 1.9 ± 0.9
Post BD	54 ± 7.1*	60.4 ± 6.9*	51.4 ± 5.8	− 3.8 ± 2.9*	− 2.6 ± 1.5*	− 1.7 ± 1.2
t test *p*	< 0.01	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05

± Denotes standard deviation. *$p < 0.05$ and ** $p < 0.01$, significant difference between disease and healthy subject groups using *t* test

Table 4 Comparison of the difference between the change in critical volume ($\mathrm{Vol_{crit}}$) from the two manoeuvres pre and post bronchodilator

	Critical volume difference (% TLC)		
	Asthma	COPD	Healthy
Deflation	8.01 ± 3.5	2.95 ± 1.2	0.82 ± 1.5
SVC	10.25 ± 3.3	3.37 ± 1.7	2.81 ± 1.4
p	> 0.05	> 0.05	> 0.05

The *p* value was obtained using a *t* test between the deflation and SVC groups (± denotes standard deviation)

Critical reactance and asthma questionnaire relationship

The asthma group included 18 patients that were used in prior publications (Kelly et al. 2012, 2013). In this group, the asthma control questionnaire demonstrated a correlation with $\mathrm{Xrs_{crit}}$ measured by the deflation method using least squares regression analysis. Repeating the analysis using $\mathrm{Xrs_{crit}}$ from the SVC maneuver in the same group, produced a model with better fit to the ACQ6 and $\mathrm{Xrs_{crit}}$ data ($R^2 = 0.63$) compared with the model calculated from the deflation maneuver ($R^2 = 0.28$) (Fig. 8).

Discussion

We have demonstrated that $\mathrm{Vol_{crit}}$ and $\mathrm{Xrs_{crit}}$ can be determined from an SVC maneuver. In addition, the pattern of falling Xrs marking the beginning of lung de-recruitment can also be clearly seen in the Xrs lung volume relationship (Fig. 3). We also demonstrated that $\mathrm{Vol_{crit}}$, from the SVC maneuver is statistically (Tables 3, 4) equivalent to previously established methods (Kelly et al. 2012, 2013). While there was a bias between measurements of $\mathrm{Xrs_{crit}}$ between the two maneuvers, the $\mathrm{Xrs_{crit}}$ from the SVC maneuver

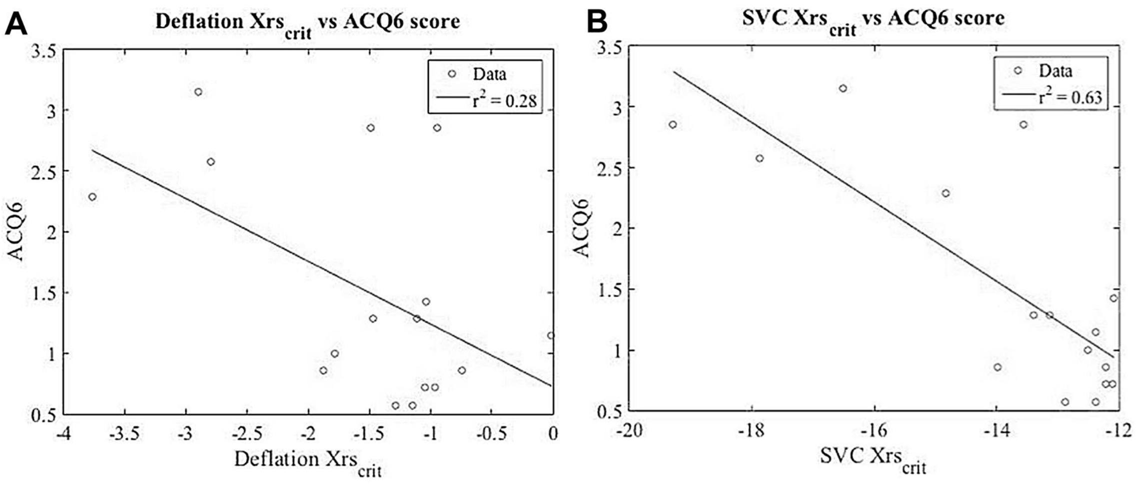

Fig. 8 Association between the 6-point asthma control questionnaire. **a** Regression analysis between subjects ACQ6 scores and $\mathrm{Xrs_{crit}}$ obtained from deflation maneuver. **b** Regression analysis between subjects ACQ6 scores and $\mathrm{Xrs_{crit}}$ obtained from SVC maneuvers

displayed a stronger relationship with asthma symptoms (ACQ) while being far simpler to perform for the subject.

The study shows that the two different breathing protocols result in a similar surrogate measurement of airway closure ($\mathrm{Vol_{crit}}$). Importantly, there was no statistical difference between the two breathing protocols when examining the changes in $\mathrm{Vol_{crit}}$ pre and post bronchodilator (Table 4). However, it is worth noting that while there was no statistical difference between the two measurements of $\mathrm{Vol_{crit}}$ it can be observed that some individual outliers displayed a large difference in lung volumes. For the asthma group, both of the methods (SVC and deflation) showed a large reduction in $\mathrm{Vol_{crit}}$ post bronchodilator which is consistent with previous studies that demonstrate changes in the airway closure following bronchodilator (Kelly et al. 2012, 2013; Irvin and Bates 2009; Samee et al. 2003; de Lange et al. 2006). Indeed for the asthma group, the post bronchodilator $\mathrm{Vol_{crit}}$ was similar to the healthy controls. However, the magnitude of the change was larger using the SVC maneuver in all groups. The SVC maneuver also yielded a statistically significant change in $\mathrm{Vol_{crit}}$. in the COPD population where the deflation maneuver did not. These results suggest that the SVC maneuver may be more sensitive to changes in $\mathrm{Vol_{crit}}$ than the deflation maneuver.

A clear proportional bias between the two measurements of $\mathrm{Xrs_{crit}}$ is observable (Fig. 7). Analysis was performed by taking the logarithm of $\mathrm{Xrs_{crit}}$ and this removed the proportional bias and left a consistent fixed bias. While there may be a bias between the two measurements of $\mathrm{Xrs_{crit}}$ they both follow the same trend as there is a clear linear trend between the two variables that is statistically significant (Table 2; Fig. 6). Therefore, even though a bias occurs when comparing the two methods of generating $\mathrm{Xrs_{crit}}$ the two methods display the similar behaviour.

A likely reason for the proportional bias and offset between SVC and deflation estimates of $\mathrm{Xrs_{crit}}$, is the effect of inhalation and exhalation, and expiratory flow limitation can have on the measurement of Xrs. At low frequencies, the inertial component of Xrs is negligible and Xrs is dominated by the elastic properties of the respiratory system and thoracic gas compressibility (Kaczka 1997, 1999; Kaczka et al. 2005). These elastic properties primarily consist of the elastic recoil of the parenchyma and respiratory tissues (Fredberg and Stamenovic 1989) with a small contribution from the chest wall (Barnas et al. 1987). The activation of respiratory muscles will alter the elastic properties of the lung and the chest wall, therefore, resulting in different values of Xrs during exhalation and inhalation. Also, if a subject suffers from expiratory flow limitation (EFL), the continued exhalation during the SVC maneuver may result in EFL. Expiratory flow limitation can result in increased negative Xrs (Dellaca et al. 2004, 2006, 2007) due to narrowing of the airways without complete closure, forming choke points (Peslin et al. 1996; Vassiliou et al. 1996). These choke points effectively block FOT signals and results in a reduced volume the FOT signals can reach. The fact that during the SVC maneuver we only analyse Xrs during the exhalation period, while the deflation maneuver contains both inhalation and exhalation could significantly contribute to the bias observed in $\mathrm{Xrs_{crit}}$ to be different during the two maneuvers.

A second possible explanation is that respiratory elastance, and its inverse compliance, has a long transient response to changes in lung volume (Lutchen et al. 2001; Williams et al. 1966; Dechman et al. 1994). Since reactance is a measure of elastance, reactance also has a transient response to changes in lung volume. It is likely that this transient response is affecting the measured Xrs differently during the deflation maneuvers and contributing to the bias in $\mathrm{Xrs_{crit}}$. To generate the Xrs lung volume relationship both of the breathing maneuvers require the subject to inspire to TLC before breathing down to RV. As a deep inspiration triggers a transient response in reactance, this will occur during both maneuvers. However, since the measurement from the SVC maneuver is conducted over a short time period, we would expect the subject to reach $\mathrm{Vol_{crit}}$ faster than from the deflation maneuver. Therefore, the transient response of reactance will have a greater effect on the result of $\mathrm{Xrs_{crit}}$ obtained from the SVC maneuver, than the deflation maneuver creating a bias.

Another contributing factor to the bias in $\mathrm{Xrs_{crit}}$ may be from a greater amount of airway closure occurring during the SVC maneuver. Previous studies suggests that airway closure occurs due to liquid bridges (Frazer and Franz 1981; Hohlfeld et al. 1999; Gaver et al. 1990) occluding the airway as well as actual mechanical collapse of the airway walls (Otis et al. 1996). Bates and Irvin (2002) demonstrated that the closure that occurs via liquid bridging has a time constant component. That is, closure of an airway is not only dependent on the volume of the lung but also the time that the lung is allowed to remain at that volume. Measuring $\mathrm{Xrs_{crit}}$ will be effected by the time that the lung is at any given lung volume. Therefore, it is likely that $\mathrm{Xrs_{crit}}$ will be different depending on which maneuver is used. As the deflation maneuver requires constant deflation and reinflation of the lung during the maneuver, less time is allowed for the liquid bridges to connect and create airway closure. The SVC maneuver is one slow constant deflation allowing longer for liquid bridges to form, resulting in a greater amount of airway closure, and therefore, a reduced $\mathrm{Xrs_{crit}}$. This increased airway closure may also explain why the SVC maneuver displayed a greater difference in $\mathrm{Xrs_{crit}}$ in the subjects with asthma, and a better correlation with ACQ6, than the deflation maneuver. Our data demonstrated a greater change in $\mathrm{Vol_{crit}}$ in the COPD group following bronchodilator using the SVC maneuver than the deflation maneuver (Table 3) and the relationship between $\mathrm{Xrs_{crit}}$ and ACQ6

(Fig. 8) was stronger using the SVC maneuver compared to the deflation maneuver.

Both methods of deriving Xrs_{crit} yielded similar results in the relationship between Xrs_{crit} and ACQ6 (Fig. 8) in the asthmatic dataset. However, even though both techniques display a similar trend, the actual values of Xrs_{crit} are different, hence the bias. Therefore, while the actual values of Xrs_{crit} may differ, they are consistently different and can be used clinically to display the same patterns. Indeed, the SVC data displayed a better fit of the data, with a much higher proportion of the variance explained by the model. The R^2 value of the SVC data ($R^2 = 0.63$) is more than double the R^2 value of the deflation data ($R^2 = 0.28$). In this case the SVC maneuver delivered better results than the deflation maneuver.

An example of the two Xrs_{crit} variables displaying the same trends is evident in the statistical difference between the value of Xrs_{crit} in the disease groups and the healthy group (Table 3). The value of Xrs_{crit} derived using both methods was statistically more negative in both the asthmatic group and the COPD group than the healthy group. However, the difference between the asthmatic and healthy group was statistically larger in the SVC-derived Xrs_{crit} ($p < 0.01$) than the deflation-derived Xrs_{crit} ($p < 0.05$). This data suggests that the SVC maneuver is likely to be more sensitive for detecting differences in Xrs_{crit} than the deflation maneuver.

A possible limitation of the study is that the asthmatic group used a different FOT recording device to the COPD and healthy groups. This was unavoidable due to the location, timing and equipment of the different testing laboratories. However, all Xrs lung volume curves and subsequent detection of Vol_{crit} and Xrs_{crit} were generated via the same custom software and algorithms from the raw exported FOT data. This should eliminate any differences in methods that might occur when generating the Xrs lung volumes curves. It is unlikely that the different hardware could impact the Xrs lung volume curves. Even if this did occur, individual subjects completed the SVC and deflation maneuvers on the same equipment. The main aim of the study was to compare results from the two maneuvers and the equipment differences between groups should not impact these findings.

Elevated airway closure is an important defect in a number of diseases. When airway closure occurs at a higher lung volume, ventilation heterogeneity (Crawford et al. 1989) is also increased (Leblanc et al. 1970; Milic-Emili et al. 2007). Moreover, if airway closure occurs above FRC, the amount of ventilated lung is reduced and may result in impaired gas exchange (Hedenstierna and Rothen 2012). It has been demonstrated that diseases that affect the peripheral airways may result in considerable airway closure, however, FEV_1 and/or airway resistance remains within normal limits (Hogg et al. 1968). Evidence is mounting that increased airway closure may be a primary functional defect in asthma (Irvin and Bates 2009) and that airway closure is also elevated in subjects with COPD (Osborne et al. 1988; Milic-Emili 2004). Therefore, the ability to measure airway closure provides additional information compared to standard spirometry.

In conclusion, we have developed an alternative technique for identifying a surrogate measure of airway closure from FOT recordings. The technique delivers equivalent and possibly more sensitive results to previous methods while being simple and easily performed by the patient. Given measurements of airway closure have clinical utility, this test has the potential to become a clinically useful tool.

Author contributions KN: Study design, data collection, analysis of results, writing of manuscript. KG: Study design, data collection, analysis of results, writing of manuscript. FT: Study design, and writing of manuscript. TW: Study design, and writing of manuscript. BRT: Study design, analysis of results, writing of manuscript.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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